SCIENCE & MEDICINE
Duplicate
TORONTO GENERAL HOSPITAL LIBRARY
Not to be removed from Hospital
R
1
H87
v.17
no.6
pt.1
Biological & Medical Serials

VOLUME 17 IN TWO PARTS—PART I NUMBER 6

THE ARCHIVES OF INTERNAL MEDICINE

LIBRARY
APR 16 1974
UNIVERSITY OF TORONTO

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston
THEO. C. JANEWAY, Baltimore
GEORGE DOCK, St. Louis
WARFIELD T. LONGCOPE, New York City
W. S. THAYER, Baltimore

JUNE 15, 1916

STORAGE

CHICAGO
AMERICAN MEDICAL ASSOCIATION
PUBLISHERS

Entered as Second-Class Matter, January 23, 1908, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879

CONTENTS OF VOLUME XVII

JANUARY, 1916. NUMBER 1

Observations on the Origin and Status of the So-Called "Transitional" White Blood Cell. Frank A. Evans, M.D., Baltimore.

Adams-Stokes Syndrome — Persistent Bradycardia Involving Both Auricles and Ventricles. Remarkable Prolongation of the As-Vs Interval. W. S. Thayer, M.D., Baltimore.

The Typhoidin Quotient. Quantitative Studies of the Cutaneous Test of Typhoid Immunity. Eugene S. Kilgore, San Francisco.

The Splenic Pathology of Pernicious Anemia and Allied Conditions. A Duodenal Method of Estimating Hemolysis. J. P. Schneider, M.D., Minneapolis.

Blood Urea Determinations in 211 Cases. Harold Schwartz, M.D., and Caroline McGill, M.D., Butte, Mont.

Serum Sickness in a Series of Five Hundred Patients Treated with Diphtheria Antitoxin. Mills Sturtevant, M.D., New York.

The Intraspinal Treatment of Syphilis of the Central Nervous System, According to the Method of Swift and Ellis. Richard Dexter, M.D., and Clyde L. Cummer, M.D., Cleveland.

Prothrombin and Antithrombin Factors in the Coagulation of Blood. George R. Minot, M.D., and George P. Denny, M.D., Boston and Daniel Davis, M.D., Baltimore.

Some Clinical Physiologic and Chemical Observations on Ptomain Poisoning from "Creamed" Codfish. M. A. Blankenhorn, M.D., G. E. Harmon, M.D., and Paul J. Hanzlik, M.D., Cleveland.

Observations on Sino-Auricular Heart Block. Samuel A. Levine, M.D., Boston.

The Effect of Continuous Electric Light in Experimental Arthritis. Walter E. Simmonds, M.D., and Josiah J. Moore, M.D., Chicago.

FEBRUARY, 1916. NUMBER 2

On Nonparasitic Chyluria. K. I. Sanes, M.D., and Max Kahn, M.D., Ph.D., Pittsburgh.

Experimental Alcoholic Cirrhosis of the Liver. Arthur L. Grover, M.D., Iowa City, Ia.

The Blood and the Blood Vessels in Hemophilia and Other Hemorrhagic Diseases. Alfred F. Hess, M.D., New York.

Eventration of the Diaphragm, with Report of a Case of Right Sided Eventration. Stanhope Bayne-Jones, M.D., Baltimore.

A Study of the Lipin Content of a Case of Gaucher's Disease in an Infant. H. R. Wahl, M.D., and M. L. Richardson, M.D., Cleveland.

The Interpretation of a Positive Nitrogen Balance in Nephritis. Herman O. Mosenthal, M.D., Baltimore, and Annabella E. Richards, Ph.D., Philadelphia.

The Permanganate Reduction Index of Cerebrospinal Fluid. W. O. Hoffman, M.D., and A. B. Schwartz, M.D., Chicago.

The Treatment of Typhoid Fever by Intravenous Injections of Polyvalent Sensitized Typhoid Vaccine Sediment. Studies in Typhoid Immunization VI. Frederick P. Gay, M.D., Berkeley, Calif., and Henry T. Chickering, M.D., New York.

The Control of Experimental Cretinism. H. Raymond Basinger, Ph.D., Chicago.

Agglutination in Pertussis, Its Characteristics and Its Comparative Value in Clinical Diagnosis, and in Determination of Genus and Species. Olga R. Povitzky, M.D., and Edward Worth, New York.

Book Review: Diabetes Mellitus. By Nellis B. Foster, M.D.

MARCH, 1916. NUMBER 3

Ventricular Hemorrhage: A Symptom-Group. Alfred Gordon, M.D., Philadelphia.

The Gastric Mucosa in Delirium Tremens. Edwin F. Hirsch, M.D., Chicago.

The Circulatory Reaction to Graduated Work as a Test of the Heart's Functional Capacity. Theodore B. Barringer, Jr., M.D., New York.

Some Attempts to Produce Exophthalmos Experimentally. Abraham Troell, M.D., Stockholm, Sweden.

The Uric Acid Solvent Power of Urine After Administration of Piperazin, Lysidin, Lithium Carbonate and Other Alkalies. Howard D. Haskins, M.D., Portland, Ore.

The Clinical Study of Edema by Means of the Elastometer. A. B. Schwartz, M.D., Chicago.

Serologic Examinations in a Case of Polycythemia. Hugo A. Freund, M.D., and Walton K. Rexford, M.D., Detroit.

On the Toxicity of Various Commercial Preparations of Emetin Hydrochlorid. R. L. Levy, M.D., and L. G. Rowntree, M.D., Baltimore.

Three Cases of Purpura Hemorrhagica in Chronic Tuberculosis. With a Brief Review. S. Bauch, M.D., New York.

Remarks on B. Welchii in the Stools of Pellagrins. William H. Holmes, M.D., Chicago.

The Archives of Internal Medicine

Vol. XVII JUNE, 1916.—IN TWO PARTS. PART I. No. 6

A STUDY OF SALT, NITROGEN AND WATER EXCRETION IN NEPHRITIS *

JAMES P. O'HARE, M.D.
BOSTON

INTRODUCTION

It has been known for a long time that in cases of chronic nephritis there is a disturbance in salt and nitrogen elimination. A number of observers have called attention to the fact that frequently the excretion of salt is disturbed proportionately more than that of nitrogen while occasionally the reverse is true. Several methods of studying these factors have been suggested.

Von Monakow[1] placed patients on a standard diet containing each day approximately the same amounts of salt, nitrogen and water, to which were added on different days a definite amount of salt (10 gm. of sodium chlorid) or nitrogen (20 gm. of urea); the daily excretion of salt, nitrogen and water was quantitated and the effects of the added salt and nitrogen were noted by comparing the excretion after these were given with the previous daily excretion. This method we will speak of as the "added urea and salt test."

Hedinger and Schlayer[2] gave on a single day to patients a diet composed of several meals containing varying amounts of the natural diuretics, water, salt, xanthin bases and caffein and collected the urine in two-hour portions throughout the day. In these portions the amounts of fluid and salt, and the specific gravity and percentage of salt were determined. For several days prior to this day the patients were on a diet containing daily approximately the same amounts of fluid, salt and protein. Hedinger and Schlayer did not quantitate the nitrogen output, but we have done so in making the test. This test we term for brevity "the two-hour renal test."

* Submitted for publication, Feb. 11, 1916.

* From the Medical Clinic of the Peter Bent Brigham Hospital, Boston.

* This work was aided in part by a grant from the Proctor Fund of Harvard University for the Study of Chronic Disease.

1. Von Monakow: Deutsch. Arch. f. klin. Med., 1911, cii, 248.
2. Hedinger and Schlayer: Deutsch. Arch. f. klin. Med., 1914, cxiv, 120.

Ambard and his associates[3] have investigated the relation between urea nitrogen and salt in the blood and urine and by means of formulas have expressed this relation as an index of excretion. More recently McLean[4] has modified and amplified these formulas of Ambard.

At the Peter Bent Brigham Hospital under the direction of Dr. Henry A. Christian I have been studying the water, salt and nitrogen elimination in chronic nephritis by one or all of these methods with the view to utilizing them as measures of the functional power of the kidney. In addition other tests of renal function have been carried out in the study of these same patients. With this data it seems worth while to report the results obtained and to discuss the relative value of some of these tests.

METHODS

The "added urea and salt test" has been carried out much as described by von Monakow. Our patients have been placed on a diet containing 75 gm. of protein, 4 gm. of sodium chlorid and 1,500 c.c. of water with a caloric value of 2,000 to 2,200.[5] After the output of fluid, salt and nitrogen reaches an equilibrium on this diet, on one day 10 gm. of additional salt is given, and several days later the patient receives 20 gm. of urea. This order may be reversed. The daily output of urine, salt and nitrogen is determined[6] and charted as shown in Figure 1.

After salt or nitrogen are added to the diet in normal individuals their excretion after forty-eight hours returns to its previous level. In the diseased kidney this may not be the case. Sometimes the added salt or urea produces a diuresis and this disturbs the elimination of both salt and nitrogen, the increased water output carrying out with it more

3. Ambard: Physiologie normale et pathologiqe des reins, Paris, 1914.

4. McLean: Jour. Exper. Med., 1915, xxii, 212.

5. Of course it is to be remembered that these values are only approximate. In the first place patients who are very sick cannot eat regularly from day to day the total food given, and daily variations arise in this way. In the second place the values as given are calculated from tables of food values and do not represent actual values determined by analyses of samples of the various meals. There must be a considerable difference between the average values stated for a given food product and the actual amount contained in a single sample of that food. Hence it is to be clearly recognized that this method of renal testing, as well as the others involving calculated diets, as carried out by us is in no sense an exact metabolic study, and variations between calculated intake and observed output are necessarily frequent. The weighing of food prepared for the patients and the subtraction of food not eaten has been done with care, and precautions have been taken to insure accurate urine collections. Errors in this part of the work have been reduced to small figures and where evident mistakes occurred in these parts of the work the results have been discarded.

6. In making the nitrogen and salt determinations I acknowledge the assistance of a chemical technician whose salary was paid from a fund given to the Medical Service of the Peter Bent Brigham Hospital by Dr. F. C. Shattuck.

salt or nitrogen. Consequently it is desirable to observe the effect of each added substance for several days after it is given before introducing the other. Then it often takes several days on the diet before salt, nitrogen and water excretion reach an approximately constant rate of excretion. These several factors render it desirable to prolong the added urea and salt test over a period of ten or twelve days, and in some cases even longer.

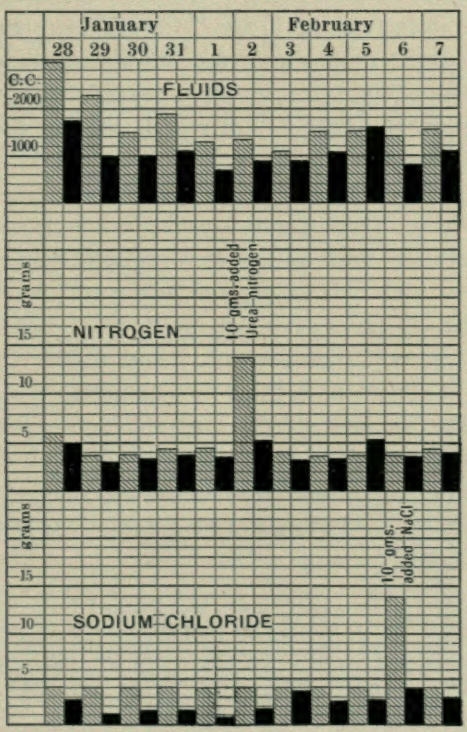


Fig. 1, Case XVI.—The hatched columns indicate intake, the cross-hatched columns output. The upper series are for fluids; the middle for nitrogen and the lower for sodium chlorid. The added salt and added urea are indicated by the lengthening of the columns of intake.

The added urea and salt test gives us rather early evidence of disturbed nitrogen and salt elimination of the kidney, as shown by delayed and deficient excretion of these substances. Simple, logical and direct as it seems, the test has many practical difficulties. In the ten or twelve days needed to carry it out the patient may tire of the hospital and refuse to stay; changes in the patient's condition may necessitate a change in diet or other interference with the conditions under which the experiment is being carried out; a woman may begin to menstruate; portions of the urine may be lost unavoidably as when the patient voids

at stool, etc., or the diet may become very monotonous. Sometimes, especially during the formation of edema, there may be a storing up of nitrogen or salt with a subsequent discharge of the same either just before or coincidently with the giving of the added urea or salt. This, of course, interferes with the correct interpretation of the changes in the excretion curves. Urea taken by mouth sometimes causes a diarrhea, with consequent probable loss of an unknown amount of nitrogen in the feces. This would have the effect of showing an apparently lower nitrogen excretion than the kidneys are really capable of handling. Of course variations in rate and completeness of absorption from the gastro-intestinal tract introduce possible errors in such dietary tests. Tissue retention, especially of salt, is another possible source of error in any such test.

On account of these various difficulties with the added urea and salt test some other form of test seemed desirable which would shorten the period of observation and reduce the probability of the difficulties enumerated above. The Hedinger and Schlayer "two-hour renal test" can be completed, as far as the patient is concerned, in twenty-four hours. In this respect, therefore, it would seem to have a decided advantage over the previous test, as by shortening the time the probability of the disadvantages enumerated above is much reduced. To compare the two tests both were carried out on a number of patients.

In using the two-hour renal test the diet has been slightly changed from that described by Hedinger and Schlayer, so that we gave the following menu for the several meals:

Seven a. m., coffee, milk, sugar, toast and butter; 10 a. m., milk, toast and butter; 12:30 p. m., bouillon, broiled steak, butter, mashed potato, butter, toast and butter, coffee, milk and sugar; 4 p. m., tea, milk, sugar, crackers; 7 p. m., soft egg, blanc mange (one egg, sugar, corn starch, milk), and cream. Amounts sufficient to give approximately 2,500 calories, 1,550 c.c. of fluid, 76 gm. of protein, 127 gm. of fat, 245 gm. of carbohydrates and 5.8 gm. of sodium chlorid.

On the two days preceding the test day the patient usually had a diet containing 2,000 calories, 75 gm. of protein and 4 gm. of sodium chlorid. The test diet is a mixed diet containing known amounts of water, nitrogen and chlorid together with food diuretics of various types (purins, salt, water, etc.). As can be seen, the diet is divided into five unequal portions given at definite times during the day. Each portion contains known but varying amounts of fluid, nitrogen and salt. The noon meal particularly contains large amounts of the above elements.

Two-hour specimens are collected from 7 a. m. to 9 p. m. and one "night specimen" is obtained containing all the urine passed between 9 p. m. and 7 a. m. Each specimen is analyzed for volume, specific

gravity, total nitrogen, nitrogen concentration, total chlorid, and chlorid concentration, and the results are charted as in Figure 2.

The purpose of the test is to find out to what extent and in what manner the diseased kidney, under stimulation by the different diuretics taken in the food, reacts in putting out the varying amounts of water, nitrogen, and chlorid ingested. Hedinger and Schlayer have shown that normal cases respond by putting out water and salt promptly and

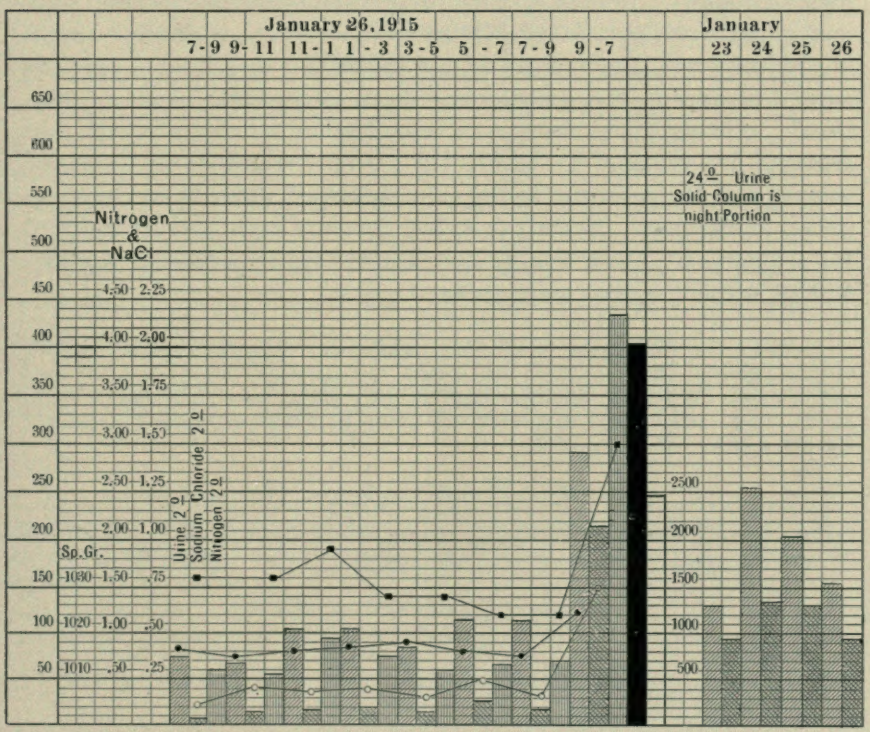


Fig. 2, Case XVI.—The series of columns beginning at the left give the amount of urine, sodium chlorid, and nitrogen in each two-hour portion from 7 a. m. to 9 p. m. and in the portion from 9 p. m. to 7 a. m. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chlorid and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

in good amounts. The diseased kidney, however, may show that its power to excrete these elements is fixed at a certain level and that this level is too low to accommodate the large amounts of these elements ingested, especially at the noon meal. These "fixed" cases show a curve of excretion that approaches more or less a straight line. Instead of getting the normal "picket fence" curves, we find some or all of the curves of excretion more or less flattened out.

CASES

In our work this year we have applied these tests to thirty cases of chronic nephritis of varying degrees of severity, some of them complicated by cardiac conditions. In one case the test was performed three times. Other tests of renal function have been made and all patients have been studied carefully to determine, in so far as is possible, their general condition. A brief summary of the records of these patients follows. In each case the "added salt and urea" and the "two-hour renal" tests are recorded in the form of charts of the type shown in Figures 1 and 2 of this paper and in Chart I to XII of a previous paper,[7] because in this graphic way the renal function is shown most clearly. Owing to the expense of reproduction the charts in each case reported are replaced by tables, but in the discussion following the summary of the cases the findings are described in terms of curves as shown in the charts. Cases 1 to 4 show no renal lesion and are included for comparison. Cases 5 to 34 show various types of chronic nephritis with or without cardiac involvement.

CASE 1.—No. 1662, male, 14, student. Diagnosis: Rheumatic fever; chronic cardiac valvular disease; aortic and mitral regurgitation. Urine: Acid; specific gravity, 1.019-1.040; albumin, none to very slight trace; no sugar. Sediment: Very rare hyaline cast with fat and cells adherent. Blood Pressure: 114-130 systolic; 46-60 diastolic.

TABLE 1.—TWO-HOUR RENAL TEST

November 4	Water, c.c.	Specific Gravity	Salt	
			Grams	Per Cent.
7 - 9 a. m.	252	1.014	1.51	0.60
9 - 11 a. m.	362	1.009	1.05	0.29
11 a. m. - 1 p. m.	95	1.017	0.35	0.37
1 - 3 p. m.	69	1.028	0.19	0.28
3 - 5 p. m.	96	1.026	0.33	0.34
5 - 7 p. m.	84	1.026	0.19	0.23
7 - 9 p. m.	57	1.029	0.21	0.36
9 p. m. - 7 a. m.	153	1.027	....	....

Summary.—Water: No fixation. Slight but somewhat delayed response to noon meal. Chlorid: No fixation. Slight but delayed response to noon meal.

7. Christian, Frothingham, O'Hare and Woods: Studies of Nephritis, Am. Jour. Med. Sc., 1915, cl, 655.

CASE 2.—No. 1755, male, aged 25, single, shoe cutter. Diagnosis: Pleurisy with effusion; tuberculosis of pleura. Urine: Acid; specific gravity, 1.010-1.029; albumin, none to the slightest possible trace; no sugar. Sediment: No casts. Blood Pressure: 130 systolic; 76 diastolic.

TABLE 2.—TWO-HOUR RENAL TEST

November 29	Water, c.c.	Specific Gravity	Salt	
			Grams	Per Cent.
7 - 9 a. m.	195	1.016	1.44	0.74
9 - 11 a. m.	133	1.022	1.30	0.98
11 a. m. - 1 p. m.	333	1.012	1.17	0.35
1 - 3 p. m.	251	1.015	1.68	0.67
3 - 5 p. m.	121	1.023	1.19	0.98
5 - 7 p. m.	126	1.019	0.79	0.63
7 - 9 p. m.	281	1.012	0.56	0.20
9 p. m. - 7 a. m.	406	1.019	1.71	0.42

Summary.—Water: No fixation. Good and prompt response to noon meal. Chlorid: No fixation. Good and prompt response to noon meal.

CASE 3.—No. 1822, male, aged 21, single, car cleaner. Diagnosis: Hyperchlorhydria. Urine: Acid; specific gravity, 1.019-1.023; albumin, none to slightest trace; no sugar. Sediment: No casts. Blood Pressure: 124 systolic, 90 diastolic.

TABLE 3.—TWO-HOUR RENAL TEST

November 6	Water, c.c.	Specific Gravity	Salt	
			Grams	Per Cent.
7 - 9 a. m.	157	1.021	1.55	0.99
9 - 11 a. m.	247	1.014	1.79	0.75
11 a. m. - 1 p. m.	310	1.011	1.40	0.45
1 - 3 p. m.	192	1.012	0.84	0.43
3 - 5 p. m.	114	1.022	1.05	0.90
5 - 7 p. m.	174	1.022	1.60	0.93
7 - 9 p. m.	155	1.019	1.10	0.71
9 p. m. - 7 a. m.	168	1.016	0.78	0.46

Summary.—Water: No fixation of amount or specific gravity. Good and prompt response to noon meal. Salt: No fixation of amount or concentration. Good response, somewhat delayed, to noon meal.

CASE 4.—No. 2656, female, aged 38, widow, domestic. Diagnosis: Syphilis; pulmonary tuberculosis (?). Urine: Acid; specific gravity, 1.006-1.018; albumin, none to slight trace; no sugar. Sediment: No casts. Blood Pressure: 106 systolic, 72 diastolic.

TABLE 4.—TWO-HOUR RENAL TEST

May 18	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	187	1.010	1.68	0.90	0.31	0.17
9 - 11 a. m.	119	1.015	0.47	0.35	0.60	0.50
11 a. m. - 1 p. m.	118	1.014	0.30	0.25	0.43	0.36
1 - 3 p. m.	80	1.023	0.48	0.60	0.59	0.74
3 - 5 p. m.	160	1.023	0.96	0.60	1.18	0.74
5 - 7 p. m.	93	1.024	0.93	1.00	0.55	0.59
7 - 9 p. m.	115	1.023	1.10	0.95	0.82	0.71
9 p. m. - 7 a. m.	295	1.025	2.36	0.80	1.03	0.68

Summary.—No fixation. Fairly good response to noon meal in all elements, slight delay in water and salt.

CASE 5.—No. 1624, male, aged 31, single, junk dealer. Diagnosis: Chronic nephritis, parenchymatous. Urine: Acid; specific gravity, 1.020-1.032; albumin, 1.2 per cent. to 2 per cent.; no sugar. Sediment: Many granular and hyaline cases. Blood Pressure: 150-127 systolic, 110-78 diastolic.

TABLE 5.—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent.	Nonprotein N_2 of Blood, Gm. per Liter
September 11	28.0	0.40
September 16	....	0.231
November 6	47.5	.....
November 16	52.5	.....

TABLE 6.—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
10/ 5	11.0	9.4	4.0	2.5	Poor response to both added urea and salt.
10/ 6	11.0	5.2	4.0	1.5	
10/ 7	21.0	11.0	4.0	2.5	
10/ 8	11.0	7.5	4.0	1.6	
10/ 9	11.0	9.5	14.0	2.4	
10/10	11.0	8.8	4.0	3.6	

TABLE 7.—Two-Hour Renal Test

November 14	Water, c.c.	Specific Gravity	Salt	
			Grams	Per Cent.
7 - 9 a. m.	74	1.025	1.32	0.95
9 - 11 a. m.	82	1.023	0.42	0.25
11 a. m. - 1 p. m.	118	1.022	0.79	0.33
1 - 3 p. m.	98	1.026	0.62	0.32
3 - 5 p. m.	128	1.024	0.63	0.24
5 - 7 p. m.	130	1.022	0.99	0.39
7 - 9 p. m.	134	1.023	0.98	0.35
9 p. m. - 7 a. m.	284	1.025	....	....

Summary.—Water: Fixation of specific gravity; none of volume. Fair response in normal time to noon meal. Chlorid: Fixation of both amount and percentage concentration with the exception of the early morning specimen. Fair response in normal time to noon meal.

Case 6.—No. 1683, male, aged 33, single, laborer. Diagnosis: Chronic nephritis; hypertension; chronic cardiac valvular disease; mitral stenosis, auricular fibrillation. Urine: Acid; specific gravity, 1.012-1.023; albumin, none to slightest possible trace; no sugar. Sediment: Rare hyaline cast. Blood Pressure: 188-160 systolic, 140-118 diastolic. Phenolsulphonephthalein in two hours: 43 per cent.

TABLE 8.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
10/2	11.0	7.0	4.0	0.9	Abnormally good response to added urea; poor response to added salt.
10/3	11.0	9.0	4.0	0.8	
10/4	21.0	15.0	4.0	1.6	
10/5	11.0	29.0	14.0	6.0	
10/6	11.0	15.0	4.0	4.5	
10/7	11.0	9.8	4.0	2.7	

TABLE 9.—Two-Hour Renal Test

Nov. 29, 1914	Water, c.c.	Specific Gravity	Salt	
			Grams	Per Cent.
7 - 9 a. m.	54	1.027	0.022	0.04
9 - 11 a. m.	50	1.025	0.01	0.02
11 a. m. - 1 p. m.	54	1.026	0.016	0.03
1 - 3 p. m.	51	1.028	0.015	0.03
3 - 5 p. m.	66	1.029	0.04	0.06
5 - 7 p. m.	69	1.028	0.06	0.09
7 - 9 p. m.	65	1.028	0.039	0.06
9 p. m. - 7 a. m.	231	1.027	0.254	0.11

Summary.—Fixation of water and specific gravity, the latter at a high level. Some fixation of concentration of salt, less of total output of salt.

Case 7.—No. 1898, male, aged 57, married. Diagnosis: Chronic nephritis; hypertension; chronic myocarditis; auricular fibrillation. Urine: Acid; specific gravity, 1.010-1.023; albumin, very slight trace to slight trace; no sugar. Sediment: Occasional hyaline and granular cast. Blood Pressure: 190-170 systolic, 130-90 diastolic.

TABLE 10.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Urea N_2 of Blood. Gm. per Liter
November 13	43.0	....
December 1	44.5	....
December 15	35.0	....
December 23	....	0.25
December 27	38.5	....

TABLE 11.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
12/20	11.2	8.0	2.9	4.4	Good response to added urea; poor response to added salt.
12/21	11.2	7.1	2.9	2.2	
12/22	20.4	13.2	3.0	3.4	
12/23	10.6	16.4	2.9	1.5	
12/24	10.6	14.4	2.9	1.0	
12/25	11.4	23.0	13.8	3.4	
12/26	10.8	10.0	2.8	2.2	

TABLE 12.—Two-Hour Renal Test

Nov. 16, 1914	Water, c.c.	Specific Gravity	Salt	
			Grams	Per Cent.
7 - 9 a. m.	138	1.015	0.50	0.35
9 - 11 a. m.	128	1.014	0.44	0.34
11 a. m. - 1 p. m.	119	1.015	0.44	0.37
1 - 3 p. m.	99	1.019	0.44	0.43
3 - 5 p. m.	110	1.019	0.58	0.52
5 - 7 p. m.	95	1.019	0.47	0.48
7 - 9 p. m.	84	1.020	0.34	0.38
9 p. m. - 7 a. m.	388	1.019	1.68	0.42

Summary.—Water: Some fixation of volume; none of specific gravity. Slight, delayed response to noon meal. Salt: Amount fixed: percentage concentration not. Slight, delayed response to noon meal.

Case 8.—No. 1918, male, aged 54, single, laborer. Diagnosis: Chronic nephritis and hypertension. Urine: Acid; specific gravity, 1.015-1.024; albumin, none to very slight trace; no sugar. Sediment: Rare granular cast. Blood Pressure: 254-200 systolic, 138-118 diastolic.

TABLE 13.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Nonprotein N_2 of Blood, Gm. per Liter
November 17	49.0	0.31
December 1	42.5	....
December 2	....	0.39
December 8	49.0	0.25

TABLE 14.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
11/23	11.0	7.5	4.0	2.4	Good response to added urea; poor response to added salt.
11/24	11.0	9.2	4.0	3.4	
11/25	21.0	12.0	4.0	2.4	
11/26	11.0	11.0	14.0	2.4	
11/27	11.0	9.0	4.0	5.0	

TABLE 15.—Two-Hour Renal Test

December 2	Water, c.c.	Specific Gravity	Salt	
			Grams	Per Cent.
7 - 9 a. m.	132	1.015	0.37	0.28
9 - 11 a. m.	67	1.019	0.087	0.13
11 a. m. - 1 p. m.	104	1.018	0.146	0.14
1 - 3 p. m.	111	1.021	0.144	0.13
3 - 5 p. m.	38	1.021	0.418	0.11
5 - 7 p. m.	122	1.022	0.146	0.12
7 - 9 p. m.	186	1.016	0.744	0.40
9 p. m. - 7 a. m.	580	1.016	2.67	0.46

Summary.—Water: No fixation. Fair but delayed response to noon meal. Chlorid: Suggestion of fixation of both amount and percentage concentration. Slight, delayed response to noon meal.

Case 9.—No. 1946, male, aged 36, married, clerk. Diagnosis: Chronic nephritis; hypertension; arteriosclerosis. Urine: Acid; specific gravity, 1.013-1.025; albumin, slight trace to large trace; no sugar. Sediment: Some hyaline and finely granular casts. Blood Pressure: 240-190 systolic, 205-140 diastolic.

TABLE 16.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Nonprotein N_2 of Blood, Gm. per Liter
November 25	49	0.28
December 8	48	....

TABLE 17.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
12/ 5	11.0	8.0	4.0	2.4	Good response to added salt. Apparently a fair response, at least to added urea.
12/ 6	11.0	8.6	4.0	2.4	
12/ 7	21.0	10.0	4.0	2.6	
12/ 8	11.0	Lost	4.0	Lost	
12/ 9	11.0	9.4	4.0	3.0	
12/10	11.0	9.9	14.0	10.0	
12/11	11.0	7.8	4.0	2.8	

TABLE 18.—Two-Hour Renal Test

November 29	Water, c.c.	Specific Gravity	Salt	
			Grams	Per Cent.
7 - 9 a. m.	93	1.023	0.065	0.07
9 - 11 a. m.	49	1.026	0.054	0.11
11 a. m. - 1 p. m.	78	1.025	0.624	0.08
1 - 3 p. m.	71	1.026	0.071	0.10
3 - 5 p. m.	71	1.025	0.085	0.12
5 - 7 p. m.	101	1.025	0.172	0.17
7 - 9 p. m.	58	1.026	0.064	0.11
9 p. m. - 7 a. m.	400	1.022	0.88	0.22

Summary.—Water: Volume and specific gravity fixed. Slight, delayed response to noon meal. Chlorid: Percentage concentration fixed. Amount fixed except in one period. Good and prompt response to noon meal.

Case 10.—No. 2006, female, aged 45, widow, domestic. Diagnosis: Chronic nephritis; hypertension; chronic myocarditis; chronic cardiac valvular disease; mitral regurgitation. Urine: Acid; specific gravity, 1.009-1.013; albumin, slight trace to trace; no sugar. Sediment: Rare hyaline and granular casts. Blood Pressure: 210-160 systolic, 100-80 diastolic.

TABLE 19.—Functional Tests

Date	Phthalein in 2 Hours	Blood Urea N_2, Gm. per Liter	Nonprotein N_2 of Blood, Gm. per Liter	Blood Chlorid,* Gm. per Liter	Alveolar CO_2, mm.
12/11	.....	....	0.80	....	.....
12/12	.....	0.67	0.95	5.36	.....
12/17	.....	0.63	0.91	5.68	.....
1/ 2	Slight trace	....	....	....	.....
1/ 7	None	....	....	....	.....
1/11	.....	....	....	....	19.09
1/14	.....	....	....	....	23.40
1/15	None	....	....	....	{41.50 {39.80
1/16	.....	....	....	....	[illegible]
1/17	.....	....	....	....	25.10

* Whole blood.

TABLE 20.—Two-Hour Renal Test

December 17	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	205	1.012	0.47	0.23	0.80	0.39
9 - 11 a. m.	192	1.012	0.33	0.17	0.67	0.35
11 a. m. - 1 p. m.	195	1.012	0.39	0.20	0.76	0.39
1 - 3 p. m.	208	1.011	0.29	0.14	0.79	0.38
3 - 5 p. m.	190	1.012	0.44	0.23	0.82	0.43
5 - 7 p. m.	215	1.013	0.43	0.20	0.99	0.46
7 - 9 p. m.	231	1.013	0.53	0.23	1.02	0.44
9 p. m. - 7 a. m.	960	1.011	1.43	0.17	4.13	0.43

Summary.—Water: Specific gravity fixed; volume partially so, Slight, delayed response to noon meal. Nitrogen: Amount fixed. Concentration somewhat fixed. Fair response in normal time to noon meal. Chlorid: Concentration somewhat fixed; amount less so. Slight, delayed response to noon meal.

Case 11.—No. 2074, male, aged 22, married. Diagnosis: Chronic nephritis. Urine: Acid; specific gravity, 1.009-1.014; albumin, 0.05 per cent. to 0.04 per cent.; no sugar. Sediment: Moderate number of hyaline and granular casts. Blood Pressure: 180-110 systolic; 140-80 diastolic.

TABLE 21.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
1/ 2	18	.....	....	....	....
1/13	13	.....	....	....	....
1/20	..	0.088	238	5.68	0.046

TABLE 22.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
1/ 5	3.9	3.5	4.0	1.4	Fair excretion of added urea. Poor excretion of added salt.
1/ 6	3.9	4.8	4.0	0.9	
1/ 7	14.4	5.4	4.0	1.1	
1/ 8	3.9	5.8	4.0	0.8	
1/ 9	3.9	4.4	4.0	0.7	
1/10	3.9	4.6	4.0	0.8	
1/11	3.9	4.2	4.0	0.9	
1/12	3.9	5.6	4.0	0.9	
1/13	....	....	14.0	2.3	
1/14	....	....	4.0	2.3	
1/15	....	....	4.0	2.8	

TABLE 23.—Two-Hour Renal Test

January 1	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	113	1 012	0.45	0.40	0.20	0.18
9 - 11 a. m.	80	1.012	0.54	0.67	0.16	0.20
11 a. m. - 1 p. m.	103	1.012	0.52	0.50	0.20	0.19
1 - 3 p. m.	107	1.012	0.50	0.47	0.26	0.24
3 - 5 p. m.	154	1.012	0.66	0.43	0.46	0.30
5 - 7 p. m.	135	1.012	0.45	0.33	0.45	0.33
7 - 9 p. m.	160	1.012	0.64	0.40	0.43	0.27
9 p. m. - 7 a. m.	450	1.012	1.67	0.37	1.08	0.24

Summary.—Water: Specific gravity fixed; volume not. Medium response in normal time to noon meal. Nitrogen: Amount and percentage concentration moderately fixed. Slight, delayed response to noon meal. Salt: Amount and percentage concentration moderately fixed. Slight, delayed response to noon meal.

Case 12.—No. 2077, female, married, housewife. Diagnosis: Chronic nephritis; hypertension; chronic myocarditis. Urine: Acid; specific gravity, 1.013-1.020; albumin, slight to very slight trace; no sugar. Sediment: Rare hyaline and granular cast. Blood Pressure: 254-202 systolic, 140-110 diastolic.

TABLE 24.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)	Alveolar CO_2, mm.
12/24	55	.....	....	....	....	....
12/28	45	.....	....	....	....	....
1/18	50	.....	....	....	....	....
1/19	..	0.225	6.45	5.85	0.13	....
1/26	..	.....	....	....	....	43.4

TABLE 25.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
1/11	11.1	6.6	4.0	1.6	Fair excretion of both added urea and salt, the former somewhat the better.
1/12	11.1	4.9	4.0	2.0	
1/13	20.1	13.0	4.0	2.4	
1/14	11.0	6.7	4.0	1.0	
1/15	*11.1	8.8	4.0	4.8	
1/16	11.0	5.5	14.0	6.3	
1/17	11.1	4.8	4.0	2.6	
1/18	....	....	4.0	3.4	
1/19	....	....	3.5	1.0	
1/20	....	....	3.0	2.8	
1/21	....	....	3.8	1.0	
1/22	....	....	3.8	1.4	
1/23	....	....	14.0	1.6	
1/24	....	....	4.0	7.6	
1/25	....	....	4.0	3.4	

TABLE 26.—Two-Hour Renal Test

December 31	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	108	1.016	0.40	0.40	0.24	0.23
9 - 11 a. m.	72	1.017	0.90	1.20	0.22	0.30
11 a. m. - 1 p. m.	53	1.021	0.37	0.70	0.11	0.20
1 - 3 p. m.	114	1.020	1.48	1.30	0.42	0.37
3 - 5 p. m.	58	1.025	0.58	1.00	0.17	0.30
5 - 7 p. m.	68	1.023	1.70	2.50	0.22	0.32
7 - 9 p. m.	60	1.025	0.96	1.60	0.22	0.37
9 p. m. - 7 a. m.	230	1.026	2.76	1.20	1.11	0.44

Summary.—Water: No fixation of volume or specific gravity. Medium response in normal time to noon meal. Nitrogen: No fixation of amount or percentage concentration. Good response in normal time to noon meal. Chlorid: Moderate fixation of percentage concentration; less of amount. Slight response in normal time to noon meal.

Case 13.—No. 2079, male, aged 23, single, student. Diagnosis: Chronic nephritis. Urine: Acid; specific gravity, 1.009-1.022; albumin, slightest possible trace to slight trace; no sugar. Sediment: No casts. Blood Pressure: 150-122 systolic; 90-60 diastolic.

TABLE 27.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Urea N_2 of Blood, Gm. per Liter
December 27.....	68.5	0.11

TABLE 28.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
12/31	11.0	11.0	4.0	2.0	Fair excretion of added urea. Apparently poor excretion of added salt.
1/ 1	11.0	10.0	4.0	2.6	
1/ 2	21.0	9.8	4.0	2.1	
1/ 3	11.0	12.0	4.0	2.0	
1/ 4	11.0	10.6	4.0	2.7	
1/ 5	11.0	9.8	14.0	5.5	

TABLE 29.—Two-Hour Renal Test

December 30	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	72	1.020	0.86	1.20	0.11	0.15
9 - 11 a. m.	128	1.014	0.90	0.70	0.28	0.22
11 a. m. - 1 p. m.	76	1.022	1.14	1.50	0.18	0.22
1 - 3 p. m.	78	1.027	1.17	1.50	0.17	0.22
3 - 5 p. m.	80	1.027	1.31	1.64	0.26	0.32
5 - 7 p. m.	68	1.026	1.09	1.60	0.17	0.25
7 - 9 p. m.	68	1.027	1.09	1.61	0.19	0.28
9 p. m. - 7 a. m.	265	1.027	4.29	1.62	0.85	0.32

Summary.—Water: No fixation except that in the afternoon, which was both of volume and specific gravity. No response to noon meal. Nitrogen: No fixation except in the percentage concentration during the afternoon. Slight response in normal time to noon meal. Chlorid: Fixation both of amount and percentage concentration. Very slight response in normal time to noon meal.

Case 14.—No. 2124, male, aged 54, married, driver. Diagnosis: Chronic nephritis; hypertension; chronic myocarditis. Urine: Acid; specific gravity, 1.013-1.016; albumin, none to very slight trace; no sugar. Sediment; no casts. Blood Pressure: 250-200 systolic, 170-100 diastolic.

TABLE 30.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean) Per Cent.	Blood Chlorid, Gm. per Liter
January 5	36	0.33	..	....
January 14	28	....	..	....
January 21	..	0.33	16	4.92*

* Whole blood.

TABLE 31.—Two-Hour Renal Test

January 21	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	22	1.026	0.21	0.94	0.018	0.08
9 - 11 a. m.	44	1.026	0.53	1.20	0.026	0.06
11 a. m. - 1 p. m.	57	1.026	0.68	1.20	0.034	0.06
1 - 3 p. m.	72	1.027	0.95	1.32	0.036	0.05
3 - 5 p. m.	78	1.027	0.89	1.14	0.047	0.06
5 - 7 p. m.	72	1.026	0.76	1.05	0.036	0.05
7 - 9 p. m.	162	1.020	1.13	0.70	0.324	0.20
9 p. m. - 7 a. m.	945	1.016	3.78	0.40	3.78	0.40

Summary.—Water: Specific gravity fixed the greater part of the day; volume not. Slight, delayed response to noon meal. Nitrogen: No fixation. Slight response in normal time to noon meal. Chlorid: Both amount and percentage concentration fixed at a low level. Very delayed response, but in good amount, to noon meal.

Case 15.—No. 2132, male, aged 35, single, cashier. Diagnosis: Chronic nephritis; hypertension. Urine: Acid; specific gravity, 1.004-1.006; albumin, slight trace; no sugar. Blood Pressure: 270-240 systolic; 150-140 diastolic.

TABLE 32.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
1/5	33	.....	....	....	....
1/8	..	0.296	9	5.7	0.01

TABLE 33.—Two-Hour Renal Test

January 8	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	327	1.010	0.82	0.25	1.37	0.42
9 - 11 a. m.	100	1.011	0.50	0.50	0.23	0.23
11 a. m. - 1 p. m.	73	1.012	0.66	0.90	0.08	0.11
1 - 3 p. m.	156	1.012	0.62	0.40	0.359	0.23
3 - 5 p. m.	170	1.012	0.56	0.33	0.51	0.30
5 - 7 p. m.	149	1.012	0.54	0.36	0.358	0.24
7 - 9 p. m.	129	1.012	0.45	0.35	0.245	0.19
9 p. m. - 7 a. m.	655	1.011	2.29	0.35	1.97	0.30

Summary.—Water: Specific gravity fixed; volume not. Good and prompt response to noon meal. Nitrogen: Amount fixed; percentage concentration not. No response to noon meal. Chlorid: No fixation of salt. Fair and prompt response to noon meal.

Case 16.—No. 2202, male, aged 49, single, painter. Diagnosis: Chronic nephritis; arteriosclerosis; hypertension. Urine: Acid; specific gravity 1.010-1.017; albumin, very slight to slight trace; no sugar. Sediment: Few granular and hyaline casts. Blood Pressure: 240-170 systolic; 160-90 diastolic.

TABLE 34.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)	Alveolar CO_2, mm.
1/21	18	.....	....	....	....	....
1/22	..	.....	....	....	....	41.9
1/26	..	0.335	16.9	6.35	0.63	....

TABLE 35.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
1/30	4.0	5.4	4.0	1.5	Poor response to both added urea and salt.
1/31	4.2	3.9	1.9	1.4	
2/ 1	4.0	3.4	4.0	0.8	
2/ 2	14.0	5.0	4.0	1.6	
2/ 3	4.4	3.8	4.0	3.3	
2/ 4	4.0	3.8	4.0	2.6	
2/ 5	4.0	5.4	4.0	2.8	
2/ 6	4.0	4.0	14.0	3.8	
2/ 7	4.2	4.0	4.0	2.8	

TABLE 36.—Two-Hour Renal Test

January 26	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	75	1.017	0.60	0.80	0.09	0.11
9 - 11 a. m.	68	1.015	0.53	0.80	0.14	0.20
11 a. m. - 1 p. m.	104	1.016	0.98	0.90	0.14	0.18
1 - 3 p. m.	105	1.017	0.72	0.70	0.20	0.20
3 - 5 p. m.	82	1.017	0.58	0.70	0.12	0.15
5 - 7 p. m.	112	1.016	0.68	0.60	0.25	0.25
7 - 9 p. m.	114	1.015	0.69	0.60	0.18	0.15
9 p. m. - 7 a. m.	290	1.025	4.36	1.50	2.17	0.75

Summary.—Water: Specific gravity and volume moderately fixed. Slight response in normal time to noon meal. Nitrogen: Amount and percentage concentration fixed. Slight response in normal time to noon meal. Chlorid: Amount and percentage concentration fixed at a low level. Slight response in normal time to noon meal.

Case 17.—No. 2218, female, aged 40, widow. Diagnosis: Chronic nephritis; chronic myocarditis; chronic bronchitis; hyperthyroidism; acute bronchitis. Urine: Acid; specific gravity, 1.014-1.023; albumin, none to trace; no sugar. Sediment: Occasional hyaline and rare granular cast. Blood Pressure: 184-160 systolic; 84-74 diastolic.

TABLE 37.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
1/30	42	.....	..	....	.....
2/18	..	0.191	81	6.1	0.217
2/23	50	.....	..	....	.....

TABLE 38.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
2/24	11.0	9.4	4.0	2.6	Good response to added urea. Fair response to added salt.
2/25	11.0	7.6	4.0	2.8	
2/26	10.4	6.6	4.0	1.8	
2/27	18.4	17.0	4.0	3.0	
2/28	11.0	6.0	4.0	1.2	
3/ 1	9.4	5.5	3.9	1.0	
3/ 2	11.1	6.0	4.0	2.0	
3/ 3	11.0	4.8	14.0	3.0	
3/ 4	11.0	7.6	4.0	6.0	

TABLE 39.—Two-Hour Renal Test

February 18	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	67	1.022	0.37	0.55	0.39	0.58
9 - 11 a. m.	74	1.020	0.23	0.31	0.50	0.68
11 a. m. - 1 p. m.	56	1.022	0.40	0.72	0.25	0.44
1 - 3 p. m.	108	1.022	0.79	0.73	0.64	0.59
3 - 5 p. m.	100	1.023	0.76	0.76	0.60	0.60
5 - 7 p. m.	101	1.024	0.58	0.57	0.53	0.53
7 - 9 p. m.	22	1.024	0.33	1.50	0.11	0.48
9 p. m. - 7 a. m.	245	1.023	0.75	0.31	1.00	0.41

Summary.—Water: Specific gravity fixed; volume not. Good response in normal time to noon meal. Nitrogen: No fixation. Medium response in normal time to noon meal. Chlorid: Both amount and percentage concentration fixed. Medium response in normal time to noon meal.

Case 18.—No. 2237, female, aged 65, single, nurse. Diagnosis: Chronic nephritis; chronic myocarditis; arteriosclerosis; mitral insufficiency; dilatation of aorta. Urine: Acid; specific gravity 1.010-1.039; albumin, none to slight trace; no sugar. Sediment: Hyaline and rare granular cast. Blood Pressure: 188-115 systolic, 110-75 diastolic.

TABLE 40.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
1/30	60	.....	....	....	.....
2/ 8	..	0.123	42.0	6.40	0.381
2/24	56	.....	....	....	.....
2/27	..	0.113	106.0	5.84	0.062
3/ 2	..	0.160	42.5	5.90	0.81

TABLE 41.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
2/14	11.0	9.5	4.0	2.2	Good response to added urea the first time; fair response the second. Fair response to added salt.
2/15	11.0	3.4+	4.0	0.8+	
2/16	20.0	17.4	4.0	4.6	
2/17	11.0	5.6+	4.0	0.7+	
2/18	11.0	9.4	4.0	1.3	
2/19	9.9	8.0	14.0	5.0	
2/20	11.0	11.2	4.0	5.4	
2/21	11.0	8.0+	4.0	1.3+	
2/22	20.0	11.2	4.0	2.0	
2/23	11.0	7.0+	4.0	1.5+	

TABLE 42.—Two-Hour Renal Test, Modified

February 8	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	157	1.020	1.62	0.97	1.48	0.94
9 - 11 a. m.	107	1.019	0.56	0.52	1.09	1.02
11 a. m. - 1 p. m.	153	1.018	0.83	0.54	1.33	0.87
1 - 3 p. m.	114	1.026	0.75	0.66	1.21	1.06
3 - 5 p. m.	85	1.026	0.65	0.77	0.83	0.98
5 - 7 p. m.	115	1.022	0.63	0.55	0.95	0.83
7 - 9 p. m.	70	1.028	0.81	1.15	0.43	0.62
9 p. m. - 7 a. m.	237	1.028	2.37	1.00	1.59	0.67

Summary.—No fixation. Water shows a medium response in normal time to noon meal. Nitrogen and salt are characterized by a slight response in normal time to noon meal.

CASE 18.—No. 2237 (continued).

TABLE 43.—TWO-HOUR RENAL TEST, CASE 18

February 27	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	223	1.010	0.73	0.37	0.54	0.24
9 - 11 a. m.	72	1.016	0.57	0.79	0.30	0.42
11 a. m. - 1 p. m.	200	1.013	0.98	0.49	0.68	0.34
1 - 3 p. m.	75	1.022	0.90	1.20	0.34	0.45
3 - 5 p. m.	130	1.021	1.48	1.14	0.62	0.48
5 - 7 p. m.	89	1.020	0.96	1.08	0.25	0.28
7 - 9 p. m.	74	1.021	0.92	1.24	0.15	0.20
9 p. m. - 7 a. m.	317	1.023	4.42	1.39	1.08	0.34

Summary.—No fixation. Water shows a good response in normal time to noon meal; nitrogen a good response but delayed; salt a medium response in normal time.

TABLE 44.—TWO-HOUR RENAL TEST

March 2	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	264	1.010	0.96	0.37	0.60	0.23
9 - 11 a. m.	87	1.017	0.70	0.87	0.43	0.51
11 a. m. - 1 p. m.	67	1.017	0.64	0.92	0.26	0.37
1 - 3 p. m.	52	1.023	0.74	1.40	0.17	0.35
3 - 5 p. m.	84	1.025	0.85	1.59	0.36	0.42
5 - 7 p. m.	26	1.022	0.29	1.12	0.48	0.18
7 - 9 p. m.	55	1.027	0.78	1.40	0.19	0.35
9 p. m. - 7 a. m.	268	1.026	4.96	1.85	0.78	0.29

Summary.—No fixation of water or nitrogen. Very slight fixation of amount of salt; less of concentration. Water: Slight, delayed response to noon meal. Nitrogen: Medium, delayed response to noon meal. Chlorid: Medium, delayed response to noon meal.

Case 19.—No. 2246, male, aged 67, married, secretary. Diagnosis: Chronic nephritis and hypertension; dilatation of arch of aorta. Urine: acid; specific gravity, 1.015-1.021; albumin, very slight trace to large trace; no sugar. Sediment: No casts. Blood Pressure: 210-90 systolic.

TABLE 45.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
1/30	..	0.20	18.2	6.55	0.76
1/31	21	0.18	....	....	....
2/25	28	....	....	....	....

TABLE 46.—Two-Hour Renal Test

January 30	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	18	.....	0.14	0.80	0.11	0.60
9 - 11 a. m.	21	.....	0.14	0.65	0.12	0.58
11 a. m. - 1 p. m.	29	1.034	0.23	0.80	0.10	0.36
1 - 3 p. m.	37	1.032	0.30	0.80	0.10	0.28
3 - 5 p. m.	30	1.032	0.30	1.00	0.08	0.28
5 - 7 p. m.	46	1.030	0.90	2.10	0.10	0.23
7 - 9 p. m.	46	1.030	0.55	1.20	0.08	0.18
9 p. m. - 7 a. m.	360	1.022	4.68	1.30	1.76	0.49

Summary.—Water: Amount fixed. Specific gravity somewhat fixed. Almost no response to noon meal. Nitrogen: Amount somewhat fixed; concentration not. Fair, but delayed response to noon meal. Chlorid: Amount fixed; concentration not. No response to noon meal.

Case 20.—No. 2292, female, aged 35, widow, clerk. Diagnosis: Chronic nephritis (?); neurasthenia. Urine: Acid; specific gravity, 1.009-1.027; albumin, none to slightest possible trace; no sugar. Sediment: No casts. Blood Pressure: 120-126 systolic; 84-92 diastolic.

TABLE 47.—Functional Tests

Date	Blood Urea N_2, Gm. per Liter	Nitrogen Coefficient (Ambard)	Blood Chlorid, Gm. per Liter
February 16	0.09	.....	....
February 18	0.11	0.061	5.85

TABLE 48.—Two-Hour Renal Test (½ Fluids) *

February 19	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	37	1.021	0.26	0.70	0.17	0.46
9 - 11 a. m.	67	1.017	0.41	0.53	0.27	0.41
11 a. m. - 1 p. m.	91	1.015	0.42	0.46	0.32	0.35
1 - 3 p. m.	37	1.028	0.43	1.16	0.29	0.78
3 - 5 p. m.	41	1.028	0.66	1.62	0.28	0.68
5 - 7 p. m.	72	1.019	0.60	0.84	0.38	0.53
7 - 9 p. m.	39	1.022	0.64	1.64	0.17	0.44
9 p. m. - 7 a. m.	152	1.025	2.49	1.64	0.61	0.40

* Patient refused part of noon meal.

Summary.—Some fixation of total output of salt and nitrogen.

Case 21.—No. 2319, female, aged 42, married, housewife. Diagnosis: Chronic nephritis; hypertension; chronic tonsillitis. Urine: Acid; specific gravity, 1.010-1.027; albumin, none to a trace; no sugar. Sediment: Rare hyaline and granular cast. Blood Pressure: 240-164 systolic, 136-100 diastolic.

TABLE 49.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
2/24	48	....	....	....	.....
2/27	..	0.10	....	....	.....
3/13	44	....	....	....	.....
3/17	..	0.12	99.5	5.94	0.138

TABLE 50.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/ 1	9.6	7.0	4.0	0.9	Fair excretion of added urea; poor excretion of added salt.
3/ 2	11.0	9.5	4.0	4.4	
3/ 3	21.0	14.5	4.0	1.0	
3/ 4	11.0	5.5	4.0	0.8	
3/ 8	9.4	4.4	4.0	0.6	
3/ 9	9.7	5.6	3.6	1.2	
3/10	8.7	8.0	13.4	3.0	
3/11	11.0	7.5	4.0	3.5	

TABLE 51.—Two-Hour Renal Test, Modified

March 17	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	150	1.011	0.80	0.53	0.26	0.17
9 - 11 a. m.	152	1.010	0.68	0.45	0.33	0.22
11 a. m. - 1 p. m.	57	1.016	0.55	0.96	0.23	0.41
1 - 3 p. m.	141	1.013	0.86	0.61	0.44	0.31
3 - 5 p. m.	72	1.018	0.71	0.99	0.34	0.47
5 - 7 p. m.	87	1.019	0.94	1.08	0.45	0.52
7 - 9 p. m.	63	1.020	0.73	1.16	0.32	0.50
9 p. m. - 7 a. m.	220	1.026	3.30	1.50	1.01	0.46

Summary.—Water: No fixation. Good and prompt response to noon meal. Nitrogen: Very slight fixation of amount, considering the enforced modification of the nitrogen at the noon meal. No fixation of concentration. Fairly good and prompt response to noon meal. Chlorid: Amount fixed; concentration not. Slight but prompt response to noon meal.

Case 22.—No. 2324, aged 45, single, saleswoman. Diagnosis: Chronic nephritis; hypertension; arteriosclerosis; syphilis. Urine: Acid; specific gravity, 1.008-1.024; albumin, none to slight trace; no sugar. Sediment: Many hyaline and granular casts. Blood Pressure: 180-190 systolic, 95-58 diastolic.

TABLE 52.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)	Alveolar CO_2, mm.
2/16	..	0.126	....	5.65	.....	....
2/18	43	.....	....	....	.....	....
3/13	64	.....	....	....	.....	....
3/25	..	0.093	65	5.93	0.259	....
3/26	54	.....	....	....	.....	43.3

TABLE 53.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/11	3.9	2.0	4.0	1.0	Rather poor excretion of both added urea and salt.
3/12	3.9	3.0	3.9	1.2	
3/13	14.0	6.4	3.9	2.8	
3/14	4.0	2.5	4.0	1.0	
3/15	3.4	3.4	4.0	1.5	
3/16	3.5	2.6	3.9	1.1	
3/17	14.1	3.5	4.1	1.0	
3/18	3.5	2.5	3.8	1.0	
3/19	4.0	2.0	3.9	0.9	
3/20	3.2	3.0	13.8	1.9	
3/21	2.6	2.0	3.0	1.9	
3/22	4.0	2.6	4.0	2.0	

TABLE 54.—Two-Hour Renal Test

March 25	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	31	1.018	0.11	0.36	0.09	0.28
9 - 11 a. m.	50	1.012	0.25	0.50	0.09	0.19
11 a. m. - 1 p. m.	110	1.011	0.30	0.27	0.28	0.25
1 - 3 p. m.	39	1.011	0.15	0.38	0.24	0.62
3 - 5 p. m.	14	1.036	0.25	1.80	0.07	0.52
5 - 7 p. m.	40	1.026	0.59	1.48	0.22	0.54
7 - 9 p. m.	48	1.021	0.35	0.73	0.24	0.49
9 p. m. - 7 a. m.	300	1.019	1.95	0.65	1.50	0.50

Summary.—Water: No fixation of volume or specific gravity. Medium response in normal time to noon meal. Nitrogen: Some fixation of amount; none of percentage concentration. Medium delayed response to noon meal. Chlorid: No fixation of amount or percentage concentration. Slight response in normal time to noon meal.

Case 23.—No. 2336, aged 68, widow. Diagnosis: Chronic nephritis and hypertension; carcinoma of the stomach (?). Urine: Acid; specific gravity, 1.008-1.022; albumin; none to very slight trace; no sugar. Sediment: Hyaline and rare granular cast. Blood Pressure: 218-168 systolic, 140-68 diastolic.

TABLE 55.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
2/18	47	0.175	50	6.38	0.26
2/23	..	0.265	157	6.05	0.334
3/13	49	.....	....	....	.....

TABLE 56.—Added Urea and Salt

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
2/28	6.0	5.0	4.0	1.4	In first test added nitrogen was put out well; added salt fairly well. In second test, with an intervening rheumatic fever, the ability to handle the added nitrogen fell off. The salt was excreted as before—only fairly well.
3/ 1	4.6	4.6	3.0	0.6	
3/ 2	15.0	14.0	3.0	1.7	
3/ 3	8.6	12.0	3.5	1.7	
3/ 4	9.0	7.0	3.7	0.4	
3/ 5	8.4	7.8	13.8	1.0	
3/ 6	9.0	6.0	4.0	2.0	
3/ 7	11.0	6.4	4.4	2.6	
3/15	8.9	3.6	3.0	2.0	
3/16	5.8	5.5	2.5	2.4	
3/17	8.8	5.0	13.7	3.5	
3/18	9.0	6.5	4.0	5.7	
3/19	6.2	5.4	2.5	2.8	
3/20	17.9	7.4	3.0	2.8	
3/21	7.8	5.8	2.8	2.2	

TABLE 57.—Two-Hour Renal Test, Modified

February 23	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	120	1.009	0.54	0.45	0.13	0.11
9 - 11 a. m.	122	1.010	0.61	0.50	0.22	0.18
11 a. m. - 1 p. m.	56	1.012	0.39	0.69	0.73	0.13
1 - 3 p. m.	50	1.017	0.50	0.99	0.10	0.19
3 - 5 p. m.	33	1.022	0.34	1.04	0.08	0.24
5 - 7 p. m.	47	1.016	0.36	0.77	0.11	0.23
7 - 9 p. m.	40	1.022	0.49	1.22	0.12	0.31
9 p. m. - 7 a. m.	192	1.021	2.30	1.20	0.58	0.30

Summary.—Water: No fixation of volume or specific gravity. Slight, delayed response to noon meal. Nitrogen: Amount somewhat fixed, concentration not. Slight response in normal time to noon meal. Chlorid: Amount and concentration somewhat fixed. Slight, delayed response to noon meal.

Case 24.—No. 2357, male, aged 52, married, piano mover. Diagnosis: Chronic nephritis and hypertension; chronic myocarditis. Urine: Alkaline; specific gravity, 1.010-1.027; albumin, none to very slight trace; no sugar. Blood Pressure: 210-180 systolic; 130-100 diastolic.

TABLE 58.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Blood Chlorid,* Gm. per Liter
February 18	52	.....	.....
February 19	..	0.397	4.391

* Whole blood.

TABLE 59.—Two-Hour Renal Test

March 2	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	123	1.021	0.96	0.48	1.09	0.89
9 - 11 a. m.	118	1.020	0.67	0.57	1.10	0.93
11 a. m. - 1 p. m.	133	1.021	0.94	0.71	1.16	0.87
1 - 3 p. m.	125	1.024	1.15	0.92	1.14	0.91
3 - 5 p. m.	120	1.022	1.42	1.18	0.98	0.82
5 - 7 p. m.	108	1.022	1.53	1.42	0.94	0.87
7 - 9 p. m.	106	1.021	1.08	1.02	0.90	0.85
9 p. m. - 7 a. m.	327	1.023	3.98	1.22	2.29	0.70

Summary.—Water: Fixation of output and specific gravity. No response to noon meal. Nitrogen: No fixation. Fair but delayed response to noon meal. Salt: Fixation of output and concentration. No response to noon meal.

Case 25.—No. 2428, male, aged 60, married, policeman. Diagnosis: Chronic nephritis and hypertension. Urine: Acid; specific gravity, 1.015-1.025; albumin, none to trace; no sugar. Sediment: No casts. Blood Pressure: 205-150 systolic, 145-95 diastolic.

TABLE 60.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)	Alveolar CO_2, mm.
3/ 3	..	.....	....	....	....	38.6
3/ 5	50	.....	....	....	....	....
3/14	61	.....	....	....	....	....
3/16	..	0.228	80.7	6.24	0.52	....

TABLE 61.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/17	11.0	9.2	4.0	1.6	Fair response to added urea. Added salt test not made. Apparently some inability to handle salt.
3/18	11.0	7.8	4.0	1.8	
3/19	21.0	9.6	4.0	1.4	
3/20	11.0	9.4	4.0	1.6	

TABLE 62.—Two-Hour Renal Test

March 16	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	33	1.028	0.57	1.74	0.05	0.16
9 - 11 a. m.	56	1.026	0.97	1.74	0.15	0.26
11 a. m. - 1 p. m.	96	1.023	1.40	1.46	0.25	0.36
1 - 3 p. m.	68	1.026	1.16	1.70	0.29	0.42
3 - 5 p. m.	120	1.026	1.81	1.51	0.80	0.67
5 - 7 p. m.	78	1.023	1.05	1.34	0.62	0.61
7 - 9 p. m.	50	1.028	0.53	1.05	0.25	0.49
9 p. m. - 7 a. m.	220	1.027	3.41	1.55	1.43	0.65

Summary.—Water: Specific gravity fixed; volume not. Moderate but delayed response to noon meal. Nitrogen: No fixation. Good and prompt response to noon meal. Chlorid: No fixation. Slight, delayed response to noon meal.

CASE 26.—No. 2429, male, aged 45, married, teamster. Diagnosis: Chronic nephritis; hypertension; chronic myocarditis; auricular fibrillation. Urine: Acid; specific gravity, 1.021; trace of albumin; no sugar. Sediment: No casts. Blood Pressure: 165-125 systolic; 120-90 diastolic.

TABLE 63.—FUNCTIONAL TESTS

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
3/ 5	39	.....	..	....	....
3/ 8	..	0.1875	..	....	....
3/ 9	41	.....	..	....	....
3/26	61	.....	..	....	....
3/30	..	0.12	65	6.25	0.44

TABLE 64.—ADDED UREA AND SALT TEST

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/18	11.0	12.4	4.0	4.8	Good response to added urea; poor response to added salt.
3/19	10.9	9.4	4.0	5.5	
3/20	21.0	17.8	4.0	3.8	
3/21	11.0	12.2	4.0	2.8	
3/22	10.8	7.8	4.0	2.4	
3/23	11.2	14.6	4.0	2.6	
3/24	10.8	13.4	4.0	1.8	
3/25	9.8	5.8	4.0	1.1	
3/26	10.6	12.2	14.0	3.8	
3/27	10.4	11.0	4.0	2.8	

TABLE 65.—Two-Hour Renal Test

March 30	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	65	1.028	1.14	1.75	0.29	0.45
9 - 11 a. m.	66	1.028	1.08	1.63	0.41	0.63
11 a. m. - 1 p. m.	62	1.030	1.07	1.72	0.35	0.56
1 - 3 p. m.	83	1.030	1.13	1.48	0.50	0.60
3 - 5 p. m.	98	1.029	1.28	1.39	0.53	0.65
5 - 7 p. m.	75	1.030	1.37	1.82	0.47	0.62
7 - 9 p. m.	66	1.032	1.23	1.86	0.36	0.55
9 p. m. - 7 a. m.	216	1.029	4.49	2.08	1.19	0.55

Summary.—Water: Fixation of volume and specific gravity with slight, delayed response to noon meal. Nitrogen: Fixation of amount and percentage concentration with slight, delayed response to noon meal. Chlorid: Fixation of amount and percentage concentration with slight delayed response to noon meal.

Case 27.—No. 2438, male, aged 35, single, blacksmith. Diagnosis: Chronic nephritis; hypertension; hemiplegia. Urine: Acid; specific gravity, 1.010-1.015; albumin 0.8 gm. to 7.0 gm. per liter; no sugar. Sediment: Occasional hyaline and granular cast. Blood Pressure: 140-155 systolic, 100-105 diastolic.

TABLE 66.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Nonprotein N_2 of Blood, Gm. per Liter
March 7	27	....
March 10	..	0.39
March 13	27	....
April 2	32	....

TABLE 67.—Two-Hour Renal Test

March 10	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	51	1.020	0.86	1.69	0.48	0.94
9 - 11 a. m.	63	1.020	0.81	1.29	0.60	0.96
11 a. m. - 1 p. m.	67	1.020	1.09	1.62	0.62	0.92
1 - 3 p. m.	77	1.021	1.17	1.52	0.69	0.90
3 - 5 p. m	95	1.021	1.50	1.58	0.86	0.90
5 - 7 p. m.	91	1.020	2.53	2.78	0.82	0.90
7 - 9 p. m.	87	1.021	1.17	1.34	0.78	0.90
9 p. m. - 7 a. m.	477	1.020	9.59	2.01	3.82	0.80

Summary.—Water: Fixation of output and specific gravity. Slight response, somewhat delayed, to noon meal. Nitrogen: No fixation. Good response, somewhat delayed, to noon meal. Salt: Fixation of output and concentration. Slight response, somewhat delayed, to noon meal.

Case 28.—No. 2444, aged 15, schoolboy. Diagnosis: Chronic nephritis (?). Urine: Acid; specific gravity, 1.011-1.015; albumin, trace to 3 gm. per liter; no sugar. Sediment: Rare granular cast. Blood Pressure: 140-110 systolic, 80-72 diastolic.

TABLE 68.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
3/ 7	62	.....	....	....	.....
3/26	61	0.106	605	5.99	0.041

TABLE 69.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/21	11.0	8.4	4.0	1.4	Good response to added urea; poor response to added salt.
3/22	10.9	5.5	4.0	1.1	
3/23	11.1	9.4	14.0	2.9	
3/24	10.9	8.4	4.0	4.2	
3/25	9.8	6.1	4.0	1.6	
3/26	10.7	7.2	4.0	1.6	
3/27	21.0	21.0	4.0	3.2	
3/28	11.0	7.7	4.0	0.5	
3/29	11.2	8.3	4.0	6.8	

TABLE 70.—Two-Hour Renal Test

March 13	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	415	1.011	1.66	0.40	1.53	0.37
9 - 11 a. m.	365	1.010	2.04	0.56	1.31	0.36
11 a. m. - 1 p. m.	142	1.018	1.12	0.79	0.54	0.38
1 - 3 p. m.	153	1.021	1.64	1.07	1.01	0.66
3 - 5 p. m.	124	1.020	1.14	0.92	0.81	0.65
5 - 7 p. m.	240	1.013	1.20	0.50	1.08	0.45
7 - 9 p. m.	56	1.022	0.69	1.28	0.60	0.47
9 p. m. - 7 a. m.	165	1.026	2.46	1.49	0.66	0.40

Summary.—Water: No fixation. Medium, delayed response to noon meal. Nitrogen: No fixation. Medium, prompt response to noon meal. Chlorid: No fixation. Slight but prompt response to noon meal.

Case 29.—No. 2449, female, aged 18, single. Diagnosis: Chronic nephritis and hypertension. Urine: Acid; specific gravity, 1.008-1.016; albumin, trace to large trace; no sugar. Sediment: Very rare hyaline cast. Blood Pressure: 258-218 systolic; 174-150 diastolic.

TABLE 71.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
3/ 9	8	.....	....	....	....
3/19	..	0.695	16.2	6.55	0.77

TABLE 72.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/10	3.4	3.0	3.8	3.1	Poor response to both added urea and salt, particularly the latter.
3/11	3.6	3.6	4.0	2.6	
3/12	2.0	3.6	2.0	3.0	
3/13	13.8	5.1	4.0	2.8	
3/14	4.0	4.0	4.2	2.4	
3/15	4.5	3.6	4.0	1.6	
3/16	3.0	3.8	13.4	3.0	
3/17	2.9	3.8	2.0	3.0	
3/18	3.8	4.7	4.0	2.6	

TABLE 73.—Two-Hour Renal Test

March 19	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	47	1.012	0.21	0.45	0.06	0.14
9 - 11 a. m.	58	1.011	0.23	0.49	0.16	0.24
11 a. m. - 1 p. m.	98	1.010	0.27	0.28	0.25	0.26
1 - 3 p. m.	108	1.010	0.37	0.34	0.37	0.34
3 - 5 p. m.	73	1.011	0.32	0.44	0.18	0.25
5 - 7 p. m.	61	1.010	0.31	0.50	0.13	0.21
7 - 9 p. m.	74	1.010	0.35	0.47	0.19	0.25
9 p. m. - 7 a. m.	430	1.009	1.81	0.42	1.12	0.26

Summary.—Fixation of all elements, both total output and percentage concentration. Slight response in normal time to noon meal in all elements.

Case 30.—No. 2473, female aged 41, married, housewife. Diagnosis: Chronic nephritis; hypertension; ventral hernia. Urine: Acid; specific gravity, 1.010-1.018 albumin, none to very slight trace; no sugar. Sediment: Rare hyaline and granular cast. Blood Pressure: 208-172 systolic, 115-83 diastolic.

TABLE 74.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
3/15	55	.....	....	....	.....
3/20	..	0.098	159	6.75	0.125
3/24	59	.....	....	....	.....
4/ 9	65	.....	....	....	.....

TABLE 75.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
4. 9	11.0	9.0	4.0	1.6	Good response to added urea; poor response to added salt.
4/10	11.0	6.4	4.0	0.9	
4/11	21.0	14.5	4.0	1.0	
4/12	11.0	9.4	4.0	1.9	
4/13	11.0	5.2	4.0	1.8	
4/14	6.0	3.5	14.0	4.9	
4/15	11.0	4.1	4.0	0.8	

TABLE 76.—Two-Hour Renal Test

April 20	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	80	1.017	0.65	0.81	0.06	0.08
9 - 11 a. m.	50	1.015	0.53	1.05	0.04	0.08
11 a. m. - 1 p. m.	42	1.020	0.54	1.28	0.03	0.08
1 - 3 p. m.	40	1.025	0.67	1.64	0.02	0.04
3 - 5 p. m.	52	1.025	0.83	1.60	0.04	0.08
5 - 7 p. m.	123	1.018	1.18	0.96	0.28	0.23
7 - 9 p. m.	108	1.020	0.94	0.87	0.42	0.39
9 p. m. - 7 a. m.	320	1.021	3.01	0.94	1.06	0.33

Summary.—Water: Shows no fixation. Medium, delayed response to noon meal. Nitrogen: Shows no fixation. Medium, delayed response to noon meal. Chlorid: Shows suggestion of fixation in both amount and concentration. Slight, delayed response to noon meal.

Case 31.—No. 2486, male, aged 63, single. Diagnosis: Chronic nephritis; hypertension; arteriosclerosis; dilatation of aortic arch. Urine: Acid; specific gravity, 1.010-1.015; albumin, slight trace to 2.5 gm. per liter; no sugar. Sediment: Occasional hyaline and granular cast. Blood Pressure: 210-140 systolic, 110-84 diastolic.

TABLE 77.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
3/14	13	....	....	....	.....
3/17	..	0.61	5.9	6.3	0.571
3/26	12	....	....	....	.....

TABLE 78.—Added Urea and Salt

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/25	10.8	10.4	4.0	2.5	Fair response to added salt. Apparently able to handle nitrogen pretty well.
	11.0	9.7	4.0	2.7	
	10.9	7.6	14.0	3.4	
	11.0	12.5	4.0	5.8	
	21.0	Lost	4.0	Lost	

TABLE 79.—Two-Hour Renal Test

March 17	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m. .	61	1.017	0.50	0.82	0.098	0.16
9 - 11 a. m.	87	1.018	0.76	0.87	0.19	0.22
11 a. m. - 1 p. m.	107	1.019	0.88	0.82	0.25	0.23
1 - 3 p. m.	113	1.018	0.90	0.80	0.26	0.23
3 - 5 p. m.	135	1.018	1.12	0.83	0.41	0.30
5 - 7 p. m.	127	1.017	1.10	0.87	0.41	0.32
7 - 9 p. m.	97	1.018	0.79	0.81	0.19	0.20
9 p. m. - 7 a. m.	38	1.020	0.30	0.80	0.17	0.44

Summary.—Water: Slight fixation of volume; moderate fixation of specific gravity. Slight, delayed response to noon meal. Nitrogen: Well-marked fixation of percentage concentration. Slight, delayed response to noon meal. Chlorid: Fixation of both amount and percentage concentration. Slight, delayed response to noon meal.

Case 32.—No. 2512, female 55, single, housekeeper. Diagnosis: Chronic nephritis; hypertension; aphasia. Urine: Acid; specific gravity 1.006-1.022; albumin, none to very slight trace; no sugar. Sediment: Rare hyaline cast. Blood Pressure: 250-142 systolic; 100-65 diastolic.

TABLE 80.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
3/22	49	.....	..	....	.....
4/ 5	..	0.125	77	6.43	0.615
4/ 7	60	.....	..	....	.....
4/30	57	.....	..	....	.....

TABLE 81.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/23	3.0	5.5	4.0	1.0	Good response to added urea; poor response to added salt.
3/24	4.2	4.0	4.0	0.9	
3/25	13.5	10.6	4.0	0.9	
3/26	4.0	6.4	4.0	1.0	
3/27	4.1	5.4	4.0	1.1	
3/28	4.1	4.6	4.0	1.0	
3/29	4.0	4.7	14.0	3.4	
3/30	4.0	4.5	4.0	4.0	

TABLE 82.—Two-Hour Renal Test

April 5	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	252	1.009	0.45	0.18	0.45	0.18
9 - 11 a. m.	150	1.009	0.38	0.25	0.44	0.29
11 a. m. - 1 p. m.	143	1.010	0.40	0.28	0.27	0.19
1 - 3 p. m.	143	1.010	0.43	0.30	0.21	0 15
3 - 5 p. m.	79	1.017	0.40	0.51	0.21	0.27
5 - 7 p. m.	105	1.019	0.62	0.59	0.51	0.49
7 - 9 p. m.	73	1.018	0.50	0.68	0,38	0.52
9 p. m. - 7 a. m.	233	1.022	1.64	0.71	1.37	0.59

Summary.—Water: No fixation of volume or specific gravity. Slight, delayed response to noon meal. Nitrogen: Slight fixation of amount. Slight, delayed response to noon meal. Chlorid: Slight fixation of amount. Slight, delayed response to noon meal.

Case 33.—No. 2548, 33, female, married, housewife. Diagnosis: Nephritis, subacute, of pregnancy. Urine: Acid; specific gravity 1.006-1.020; albumin, very slight trace; no sugar. Sediment: Very rare hyaline, granular and cellular cast. Rare red blood corpuscle. Blood Pressure: 158-118 systolic; 98-66 diastolic.

TABLE 83.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
3/28	65	.....	....	....	.....
3/29	..	0.094	215	5.9	0.207
4/ 3	55	.....	....	....	.....
4/14	52	.....	....	....	.....

TABLE 84.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
4/1	11.0	8.6	4.0	2.2	Good response to added urea; poor response to added salt.
4/2	9.8	7.6	4.0	2.2	
4/3	21.0	17.0	4.0	2.6	
4/4	10.9	11.0	4.0	2.2	
4/5	10.8	10.5	4.0	1.4	
4/6	10.7	5.6	4.0	1.1	
4/7	10.0	13.0	14.0	4.0	
4/8	11.0	9.6	4.0	4.0	

TABLE 85.—Two-Hour Renal Test

March 29	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	164	1.010	0.87	0.53	0.15	0.09
9 - 11 a. m.	75	1.015	0.53	0.71	0.10	0.13
11 a. m. - 1 p. m.	193	1.008	0.63	0.33	0.17	0.09
1 - 3 p. m.	48	1.025	0.67	1.42	0.16	0.33
3 - 5 p. m.	64	1.018	0.70	1.10	0.09	0.14
5 - 7 p. m.	80	1.022	2.14	2.68	0.23	0.29
7 - 9 p. m.	48	1.023	0.50	1.05	0.05	0.10
9 p. m. - 7 a. m.	265	1.026	5.57	2.10	0.45	0.17

Summary.—Water: No fixation. Good and prompt response to noon meal. Nitrogen: No fixation. Good but delayed response to noon meal. Salt: Amount fixed; concentration not. Practically no response to noon meal.

Case 34.—No. 2567, male, 30, married, enamel worker. Diagnosis: Chronic nephritis; hypertension; chronic valvular disease; mitral insufficiency; albuminuric retinitis. Urine: Acid; specific gravity 1.006-1.011; albumin, 2 to 3.5 gm. per liter; no sugar. Sediment: Many hyaline and granular casts. Blood Pressure: 195-170 systolic; 145-140 diastolic.

TABLE 86.—Functional Tests

Date	Phthalein in 2 Hours, Per Cent.	Blood Urea N_2, Gm. per Liter	Urea Index (McLean), Per Cent.	Blood Chlorid, Gm. per Liter	Chlorid Difference (McLean)
3/30	Trace	.....	..	....	.....
4/ 5	.....	0.575	5	6.18	0.422

TABLE 87.—Added Urea and Salt Test

Date	Nitrogen in Grams		Salt in Grams		Summary
	Intake	Output	Intake	Output	
3/ 7	11.0	8.9	4.0	2.2	Apparently a good response to added urea, but a poor one to added salt.
3/ 8	11.0	9.1	4.0	2.3	
3/ 9	11.0	12.2	4.0	2.3	
3/10	21.0	Lost	4.0	Lost	
3/11	11.0	15.5	4.0	2.4	
3/12	11.0	6.9	4.0	1.4	
3/13	11.0	9.3	4.0	1.4	
3/14	11.0	10.0	4.0	1.4	
3/15	11.0	13.4	4.0	1.4	
3/16	11.0	9.4	14.0	1.3	

TABLE 88.—Two-Hour Renal Test

April 5	Water, c.c.	Specific Gravity	Nitrogen		Salt	
			Grams	Per Cent.	Grams	Per Cent.
7 - 9 a. m.	85	1.017	0.68	0.80	0.07	0.07
9 - 11 a. m.	67	1.017	0.54	0.84	0.07	0.07
11 a. m. - 1 p. m.	78	1.017	0.70	0.90	0.08	0.10
1 - 3 p. m.	78	1.017	0.65	0.85	0.10	0.15
3 - 5 p. m.	104	1.017	0.83	0.80	0.17	0.17
5 - 7 p. m.	110	1.016	0.75	0.68	0.25	0.23
7 - 9 p. m.	125	1.016	0.79	0.65	0.26	0.22
9 p. m. - 7 a. m.	520	1.015	2.91	0.57	1.05	0.20

Summary.—Water: Amount and specific gravity moderately fixed. Slight, delayed response to noon meal. Nitrogen: Amount and percentage concentration both fixed. Slight, delayed response to noon meal. Salt: Amount and percentage concentration fixed at a low level. Slight delayed response to noon meal.

RESULTS OF THE TWO-HOUR RENAL TEST

An analysis of the results given above for the cases of nephritis shows that the curves of water, nitrogen and chlorid excretion in a given case are on the whole, very similar. This is especially true in the comparison of the curves of water and chlorid output. Twenty-six out of thirty-two curves analyzed are almost complete counterparts as far as these two factors go. The remaining six are almost parallel, two being completely so in the afternoon. This would tend to show that, in the diseased kidney at least, water and salt obey very similar laws of excretion. The water and nitrogen curves are not so closely parallel. However, in thirteen out of twenty-six cases they are nearly parallel and in only two of the remaining thirteen are they very different.

With the two-hour renal test the diseased kidney shows its loss of function in several different ways, dependent on the severity of the case. Any combination of the following may be obtained. There may be general lowered excretion of water, nitrogen and salt throughout the test. As is expected, the very low outputs occur in the more severe types. There may be hypersensitivity. In certain mild cases the kidneys show hypersensitivity, especially in the morning, by putting out an abnormal amount of any or all of these elements for one or two periods. This is frequently associated with an afternoon fatigue. In cases displaying this latter condition the kidneys seem to do fairly well until they are crowded by the products of the heavy noon meal. Of course, the severe cases show fatigue all the time, if you wish to call it such. But I am referring here particularly to the mild cases that com-

ply with the foregoing. Then there may be a decreased or delayed response to the noon meal or there may be fixation, more or less complete, in the curve of excretion of any or all three elements. In these cases the power of excretion is fixed at a definite level and even the large noon meal cannot increase the height of this level. As a result we have a flattening out of the various curves.

With these possibilities in mind let us see what our cases have shown by the two-hour renal test.

WATER EXCRETION AS SHOWN BY THE TWO-HOUR RENAL TEST

The output of water in thirteen out of thirty-two tests performed on cases of nephritis (41 per cent.) approached fairly closely to the normal. These cases on the whole were of a fairly mild type or were complicated by cardiac conditions. Five out of the thirty-two tests showed a very moderate, and fourteen, a distinctly low, output. The larger number of the cases, therefore, showed a lowered excretion of water. Only two cases showed well-marked hypersensitivity. Five showed a distinct afternoon fatigue. Nineteen out of thirty-two (59 per cent.) showed a slight response to the noon meal, ten (31 per cent.) a medium response, and only three (9 per cent.) a good one. Twenty cases (63 per cent.) were characterized by a distinct delay in the time of response, whereas twelve (37 per cent.) were normal in this respect. The large majority of those showing a medium or slight response were characterized also by a delayed response.

Ten out of thirty-two tests (30 per cent.) showed a distinct fixation of both volume and specific gravity. Six (19 per cent.) showed a fixation of specific gravity with more or less variation in volume. In these, the concentration power was apparently impaired. In this group it was noticed that the two most severe cases showed a fixation at a low level, whereas the other four, which were less severe or were complicated by myocarditis, showed a fixation at a higher level. Another group of two cases showed a somewhat different condition. In these the volume remained fixed but the specific gravity varied. Here the concentrating function was apparently preserved. One of these (and possibly both) was a case of myocardial insufficiency. A group of fourteen (44 per cent.) all comparatively mild, showed no fixation whatsoever.

SALT EXCRETION AS SHOWN BY THE TWO-HOUR RENAL TEST

The large majority of the curves, from cases of nephritis, twenty-six out of thirty-two (81 per cent.), showed a low output of sodium chlorid. This is a considerably greater number than those with low water excretion. Five (16 per cent.) showed a medium, and only one

(3 per cent.) a high, excretion of salt. Three showed definite hypersensitivity. Ten (31 per cent.) tired in putting out the salt during the afternoon. With regard to the noon meal, in twenty-six cases (81 per cent.) there was only a slight response. In six the response was medium, and in none was it normal. Twenty cases (63 per cent.) showed a distinct delay in response to the large noon meal. Seventeen out of thirty-two showed almost complete fixation both of amount and percentage concentration of salt. Most of these, too, had a low output and low concentration. In nine there was a fixed amount but a varying percentage; in all but one of these the fixation was low. These retained, at least to a certain degree, their power of salt concentration. Only five showed no fixation whatsoever. This is in contrast to fourteen cases in which the water output showed no fixation.

NITROGEN EXCRETION AS SHOWN BY THE TWO-HOUR RENAL TEST

Nitrogen excretion seems to be much less affected than either salt or water excretion. Only twenty-six determinations were made. Eight showed a low, eleven a medium, and seven a fairly normal, output. Four displayed fairly well marked hypersensitivity. Only five showed afternoon fatigue. Fourteen patients showed only a slight response to the noon meal, seven a medium, and five a good, response. In seventeen cases there was a distinct delay in putting out the increased nitrogen ingested at the noon meal. The rest were normal. Only seven cases were characterized by marked fixation. These were the most severe cases studied. Six showed a fixation of amount but not of concentration. In thirteen there was no fixation at all.

DISCUSSION OF EXCRETION OF WATER, SALT AND NITROGEN AS SHOWN IN THE TWO-HOUR RENAL TEST

As can be seen from the foregoing, the chlorid excretion of the kidney is more seriously, and presumably more quickly, affected than either of the other two functions. The excretion of water and total solids runs fairly close to the chlorid excretion. The ability of the kidney to handle nitrogen however, seems to be maintained considerably longer than the other two elements. This bears out our observations in other tests that the excretion of salt is usually impaired sooner than that of nitrogen, and that when both are affected in a given case the impairment of the nitrogen excretion is less marked than that of the salt.

We have been led to believe that the most significant parts of the test are the response to the noon meal and the degree of fixation in the curves. However, the delicacy of the test is vouched for by the fact that not a single case of chronic nephritis, no matter how mild, failed

to show in one or more elements (water, salt and nitrogen) some disturbance of function such as hypersensitivity, fatigue, etc. Many of the milder cases, too, were normal in function as far as other tests like the phenolsulphonephthalein, blood urea, etc., could indicate. However, it must be borne in mind that normal cases may show, temporarily at least, these slight disturbances of function.

Putting the various curves in each case together, certain observations as to the severity of the disease can be made out. As to the amount of response, seven of the nine cases that showed only a slight response in all three elements were severe. The time of response seemed less important. Seven showed a delayed response in all three elements. Two of our most severe cases, however, showed no delay whatsoever, and three that did show delay were comparatively mild.

Fixation seems to be the most important part of this test. From the point of view of fixation in all three elements, it is seen that in our six worst cases the fixation was marked in both amount and percentage concentration. In only two was there no fixation whatsoever. These were extremely mild cases. Even in these, however, the test showed abnormal function by afternoon fatigue, delayed response, etc. Between these two groups of extremes, the cases display varying amounts of fixation in excretion of one or more elements—the more severe the greater the fixation.

It was thought that those cases complicated by cardiac conditions might be characterized in a special way. This, however, was not found to be true always. Some did show a high level of fixation in volume of urine and specific gravity with a low level of concentration and amount of sodium chlorid. These may have been more truly cases of myocardial insufficiency with added renal involvement. However, we were not convinced that this was characteristic of cardio-renal cases.

The test is by no means without faults. The most important is that it cannot be used in all cases of chronic nephritis. In very severe cases, of course, no such diet can be taken even when the heavy noon meal is modified, as was done by us for some patients. This, of course, may interfere more or less with our results, inasmuch as the reduction in the meal may just fail to show fixation when the full meal would do so.

In some cases the patient is made temporarily worse by the full diet. Then, too, digestive disturbances, indicated by distress after the noon meal, may cause a delayed absorption in the stomach and intestines. The various elements then get to the kidneys slowly and in small amounts. This would, of course, interfere with the proper interpretation of results. Cases with edema cannot be studied very satisfactorily because of the unstable water metabolism.

COMPARISON OF TWO-HOUR RENAL TEST AND ADDED UREA AND SALT TEST

To try out the comparative efficiency of the two-hour renal test and the added urea and salt test and to see if the former could supplant the latter, we can compare the results of both tests made on the same patient in twenty-one cases of chronic nephritis. Of these, five had no nitrogen determinations in the two-hour test because at that time we were not quantitating the nitrogen.

The very nature of the tests prevented their being done synchronously. The two-hour renal test was usually made either just before or just after the other test, As a result there were frequently several days between the two tests. Despite this fact, however, there was a surprisingly close parallelism between the results obtained by both methods. Of the twenty-one cases all but two showed pretty complete agreement in all phases. One of these (Case 26) showed an excellent response to added urea but a distinct fixation of nitrogen output in the two-hour test. The fixation, however, was at a high level and may have been accounted for by the fact that the patient had at this time a changed circulation from chronic myocarditis and auricular fibrillation. (McLean's urea index showed fair ability to handle nitrogen). The second case (Case 32) showed the same functional result. The patient had been on a low-protein diet preceding the added urea. This may have caused a temporary improvement in her nitrogen function, which had again become weaker when the two-hour renal test was made about one week later. (In this case, too, McLean's urea index showed fair ability of the kidney to handle nitrogen.)

COMPARISON OF THE DIETARY TESTS WITH THE INDICES OF NITROGEN AND SALT EXCRETION

The objections to these dietary tests cited above make it evident that they are not entirely satisfactory. The methods of obtaining the indices of urea and salt excretion as worked out by Ambard and McLean and others obviate many of these difficulties because they do not necessitate fixed diets and prolonged quantitative observations. It is interesting to see how the results obtained from the dietary tests compare with those furnished by the indices of excretion. In fifteen patients both of the dietary tests were made and the indices of excretion were calculated. In addition, the phenolsulphonepthalein excretion was observed. The blood urea-nitrogen and the blood chlorid figures were known so that these might be used to check up the value of the other methods.

Of course a comparison of such results presents many difficulties but a study of these cases (Cases 11, 12, 16, 17, 18, 22, 23, 25, 26, 28, 29, 30, 31, 32 and 34) will show how far the various tests agree and to

a certain extent which test seems to give uniformly the best index of the condition of the patient as judged from the sum total of observations on the patient. The phenolsulphonephthalein output and blood urea figures seem to agree pretty well. In a number of cases they are almost normal and yet the other tests give evidence of functional disturbance.

The question of the comparative values of these tests narrows itself down to a determination of whether the shorter and simpler nitrogen and salt tests of Ambard or McLean are as satisfactory as the more difficult and complex dietary tests of von Monakow and Hedinger and Schlayer. When we compare these tests in our group of cases we note that in two cases (Cases 11 and 18, March 2) the two-hour renal test shows us a greater disturbance of salt excretion than is indicated by the indices of excretion. However, the difference is marked only in one. On the other hand in two more cases (Cases 25 and 32) the opposite effect is noted, the indices of excretion indicating a greater impairment of function. With regard to nitrogen function we find that in only one (Case 11) does the two-hour renal test show greater renal disturbance than does the index of urea excretion. The determination of the index of excretion brings out distinctly greater loss of function in six other cases than is indicated by the dietary tests. In the other patients the results of the two tests are about the same.

It would seem from this that the indices of urea and salt excretion, especially the former, as determined by Ambard's or McLean's formulas, are more satisfactory tests of renal function than the others here referred to, as they give us as much information as any of the other tests, especially in the milder cases; they are distinctly shorter than the dietary tests since they can be completed in two hours, if necessary, and they are not especially difficult to carry out. The phenolsulphonephthalein excretion, to be sure, is less difficult of determination than any of these but it is by no means as satisfactory in cases of chronic nephritis because in the earlier stages of the condition it may be essentially normal although there are definite disturbances in salt, nitrogen or water excretion. A simple determination of blood nitrogen similarly may give normal figures in milder cases, while the calculated index of excretion is distinctly abnormal. For the determination of these indices of excretion no dieting or preliminary preparation is required and the determinations can be made on all but moribund patients. Hence they have an advantage over the longer dietary tests. More investigation, however, is still needed for a proper understanding of a number of factors which seem to influence the index of excretion apart from the renal lesion. One of these factors is the influence of the amount of water excretion on the index of excretion of urea or salt in a given individual. This phase of the subject is at present under

investigation. The factors which lead to very high indices of urea excretion too are not thoroughly understood at present. These and other points must be studied before the indices of excretion can be used with complete satisfaction in the study and subsequent dietary arrangement of our cases of chronic nephritis.

SUMMARY

Several methods have been proposed for the study of salt and nitrogen excretion in chronic nephritis. In one method, with the patient on a standard diet, the elimination of an added amount of salt and nitrogen is followed for several days; in another, the salt and nitrogen excretion is quantitated for one day in two-hour urine specimens with the patient on several standard meals of varying composition. A third way is to quantitate salt and nitrogen in the blood and urine and express their relations by a formula giving an index of excretion. In thirty cases the first two tests have been carried out along with other tests of renal function. The second, or two-hour renal test as we have called it, requires a shorter observation in the hospital and the main part of the test occupies only twenty-four hours of the patient's time, while the first, or added urea and salt test, requires ten or twelve days of hospital observation on a standard diet. The shorter test appears to yield almost the same facts as the longer. In general, salt excretion is impaired before there is much disturbance of water and nitrogen excretion; in most patients salt and water excretion behave very similarly; the nitrogen excretion is greatly impaired usually only in the severe cases. Salt, water and nitrogen excretion show some disturbance in even the very mild cases in which phenolsulphonephthalein excretion is normal, and there is no increased blood nitrogen. These dietary tests can not be used in all cases of chronic nephritis. They cannot be carried out in those that are very severe. The methods involving the determinations of the indices of excretion of urea and salt do not have a number of the difficulties met with in carrying out the dietary tests. These indices were determined in fifteen cases in which both dietary tests were carried out, and the indices seemed to give as much information as the other tests and to possess distinct advantages inasmuch as they can be determined for practically every patient and require considerably less time and less labor in their execution. The great advantage of all three of these tests is that they give information as to disturbed renal function in those mild cases in which phenolsulphonephthalein excretion is normal and the blood urea-nitrogen is not increased.

EXPERIMENTAL HYPERCHOLESTEROLEMIA *

KAETHE DEWEY, M.D.
CHICAGO

In previous experimental work[1] a watery colloid emulsion of cholesterol was used and proved to be such a satisfactory preparation for intraperitoneal injections in rabbits and guinea-pigs, that I employed it again as most suitable for producing a direct hypercholesterolemia. The use of such emulsions eliminates some of the objectionable features attending the prevalent method of administering cholesterol by feeding. The necessity of resorting to solvents such as fats and oils involves the production of a fat infiltration which, although not considered as pathological, necessarily masks the effects of cholesterol on the tissues to some extent and complicates the conclusions.

Instead of Merck's pure cholesterol, I used a preparation obtained from gallstones by extraction with ether in the Soxhlet apparatus. For the separation of all saponifiable substances from this ether extract, a method was employed which is based largely on Kumagawa and Sutro.[2] Five grams of the dried ether extract are dissolved in 350 to 400 c.c. of petroleum ether; to this, 70 c.c. of a 1 per cent. absolute alcoholic solution of potassium hydroxid and 30 c.c. of distilled water are added. The mixture is shaken and the ether solution of cholesterol separated from the alcoholic solution of soaps in the separating funnel. The petroleum ether is evaporated and the dry cholesterol treated in the same manner a second and, if necessary, a third time. It is finally recrystallized with alcohol. The melting point of this preparation was between 146 and 147 C. (294.8 and 296.6 F.).

In order to make a watery colloidal emulsion from this crystalline substance by the method of Porges and Neubauer[3] cholesterol is dissolved in acetone and added in small amounts to large quantities of distilled water while stirring. The acetone is evaporated and another portion of the acetone solution is added, the acetone evaporated, and so on, until all the cholesterol necessary for the desired strength has been used. The emulsion is finally filtered through an asbestos filter. When large quantities of this preparation and rather high concentra-

* From the Pathological Laboratory of Rush Medical College and the Otho S. A. Sprague Memorial Institute, Chicago.

1. Dewey and Nuzum: The Effect of Cholesterol on Phagocytosis, Jour. Infect. Dis., 1914, xv, 472.

2. Kumagawa and Sutro: Bestimmung des Cholesterins nebst den anderen unverseifbaren Substanzen, Biochem. Ztschr., 1908, viii, 315.

3. Porges and Neubauer: Physikalisch chemische Untersuchungen über das Lecithin und Cholesterin, Biochem. Ztschr., 1907, vii, 152.

tions are needed, as for example in these experiments, this method is not ideal, as it consumes an enormous amount of time. The chief difficulty was in getting all of the cholesterol into the state of a fine emulsion; some of it frequently floated on top as "foam." The observation, however, that this so-called foam when taken up with fresh acetone will easily and quickly go into the emulsion, *whether or not acetone is still present,* led to the modification of the method.[4] To a concentrated solution of cholesterol in acetone, warm distilled water is added slowly until the acetone solution, when heated, does not turn clear again. Enough acetone is added to redissolve the precipitate. The clear solution is then slowly poured into warm distilled water. If some of the cholesterol foams out, it is taken up with acetone and added to the emulsion. It is then boiled in small quantities and filtered through an ordinary fine filter paper, using a fresh paper for every new portion. The total is reduced to the desired strength by vacuum distillation and the emulsion finally refiltered.

The making of such an emulsion is time consuming, but, when once made, it is an exceedingly satisfactory preparation. Its chief virtue is its great stability. Such emulsions have been kept for three months and longer without undergoing any apparent change. Heat does not affect them; they can be sterilized in the autoclave repeatedly. They were tested by adding serum and fresh blood from normal and cholesterolized rabbits as well as physiological salt solution. By none of these fluids was the cholesterol precipitated out from its colloidal state. Whatever the ultimate fate of the colloid cholesterol in the blood, it is evidently carried off by the blood stream from the place of the injection without leaving any deposits there. It was thus possible, for example, to make thirty injections in daily succession into the veins of the ears of one rabbit. After intraperitoneal injections, cholesterol deposits in small nodules were generally found on the mesentery, liver, spleen and the under surface of the diaphragm.

The experiment consisted of intraperitoneal or intravenous injections of emulsions of cholesterol into twelve rabbits. Control animals received injections of distilled water from which the added acetone was evaporated.

It seemed proper to assume that the finer the state of division of the colloid cholesterol in the emulsion the better would be the rate and degree of absorption. To test this, three rabbits were injected intraperitoneally with emulsions which had not been filtered, and which ranged between 2 and 5 per cent. in concentration. Two of them received seven injections of respectively 20 c.c. and 10 c.c. and were killed eleven days after the first injection. The third animal was

4. Dewey, Kaethe: The Preparation of Colloidal Emulsions of Cholesterol, Tr. Chicago Path. Soc., 1915, ix, 321.

injected once with 10 c.c. of a 5 per cent. emulsion and was killed five days later. The first two animals had lost in weight at the end of the experiment. The postmortem examination showed that some of the cholesterol had not been absorbed; it was deposited in small nodules, 2 and 4 mm. in diameter, chiefly on the liver, spleen and under surface of the diaphragm. The microscopic examination gave convincing evidences that such emulsions are violent in their effect on the tissue, especially on that of the liver. In all three rabbits lesions were found in this organ which have something of the character of an infarct or sequestrum; they are sharply demarcated areas of sometimes considerable dimensions, showing marked destruction of the liver structure and enormous deposits of cholesterol in the center, surrounded by a zone of rarified tissue and an outer zone of dense round-cell infiltration. Undoubtedly these deleterious effects of the colloidal cholesterol are due to physical properties, that is, to the presence of large droplets and so-called foam and to the high concentration. Such lesions were not produced by finely filtered emulsions of low or moderate strength, which were employed in all subsequent experiments. Only in one rabbit with previously existing senile changes were similar foci found in the liver; they were, however, few in number and small in dimensions.

Three rabbits were injected intraperitoneally with doses of 10 c.c. of a 2 per cent. emulsion, two of them three times a week for a period of three and five months and the third every day for two months. The first two animals showed a gain in weight at the end of the experiment; the third rabbit lost in weight and was somewhat dull during the last two weeks.

Two rabbits of another group were injected intravenously, one with 5 c.c. of a 1 per cent. emulsion three times a week until sixteen injections were given, the other with a daily injection for thirty days, the first ten doses being 5 c.c., the last twenty doses 10 c.c. of a 1 per cent. emulsion. Both remained well during the entire period and gained in weight.

One rabbit received in daily succession thirteen intravenous injections of 10 c.c. of a 1 per cent. emulsion, and ten intraperitoneal injections of 10 c.c. of a 2 per cent. emulsion. It was killed ten days after the last injection. The animal was well until the latter part of the experiment, when there was loss of appetite for several days and loss of weight.

For comparative studies a rabbit was included in the list which showed bowel and urinary disturbances when it was received and which died after four intravenous injections.

Finally, two rabbits were injected intravenously for short periods followed by longer free intervals; at the very end a few intraperi-

toneal injections were given in quick succession. The entire experiment covered 108 days. They gained in weight and only toward the end showed lassitude and loss of appetite.

All animals were killed by air embolism.

Except in the case of the first three rabbits, which were used in a somewhat preliminary experimental way, the serum or whole blood, the bile, and in several instances also the urine, were analyzed for their cholesterol content. The method used was that of Autenrieth and Funk.[5] The chloroform solutions from the various fluids were evaporated down to 5 and 10 c.c.; 5 c.c. of these were tested. The reading was done by a Duboscq colorimeter. For histological examination pieces from various organs were fixed in 10 per cent. formalin and frozen sections from the kidney, liver, aorta, spleen, adrenal and gallbladder were examined with the polarizing microscope and stained with sudan III. Pieces from various regions of all the kidneys were also prepared for paraffin sections.

In the following tables the histological changes reported are summarized, together with data of the manner, quantity and duration of the injection and figures of serological examinations. They may be helpful in illustrating the extent and the inequality of the effects of cholesterol on various organs of the rabbits. The table of the colorimetric estimation of the cholesterol content of the blood, bile and urine is not complete and, in my opinion, cannot be used as a basis for comparative inferences of any real value. The blood was examined only once, that is, shortly before the animals were killed. I am therefore not in a position to make any statements regarding the length of time during which the cholesterol injected into the blood is retained therein or in what ratio it is passed through the liver and eliminated with the bile. To all appearances, Weltmann and Biach's[6] belief that a substance, such as cholesterol, which gains access into the blood serum of rabbits, cannot be eliminated, is not confirmed through my experiments. If it were so, the cholesterol content of the blood should be very much higher, at any rate in those rabbits which were injected intravenously.

There is one constant factor in the figures of the table which is of interest because of contradictory statements concerning this in literature. In all rabbits, normal, control and cholesterolized, the cholesterol content of the serum is decidedly less than that of the

5. Autenrieth and Funk: Ueber kolorimetrische Bestimmungsmethoden: Die Bestimmung des Gesamtcholesterins im Blut und in Organen, München. med. Wchnschr., 1913, lx, 1243.

6. Weltmann and Biach: Zur Frage der experimentellen Cholesteatose, Ztschr. f. exper. Path. u. Ther., 1913, xiv, 367.

whole blood. Some authors hold the view that it is immaterial whether one or the other is used for quantitative estimation of the cholesterol content of the blood, because this is nearly the same in both fluids. My observation to the contrary agrees with the results of Abderhalden's[7] investigations of the relative quantities of cholesterol, as well as all the other constituents of the blood, in serum, whole blood and blood corpuscles.

From the results in rabbits of the experimentally produced hypercholesterolemia, I venture to draw the following conclusions:

1. Very small quantities of cholesterol administered by intravenous injections, and relatively small amounts injected intraperitoneally, are sufficient to produce pathologic conditions in some organs of the rabbit.

2. In intermittent hypercholesterolemia, such as is produced by periodical intravenous injections of small doses, the extent of the cholesterol infiltration and other pathological conditions are entirely out of proportion to the amount of cholesterol injected.

3. Unfiltered emulsions, that is, those in which the colloid particles are heterogeneous in size, and emulsions of high concentration, have a violent destructive effect on the structures of the liver.

4. Cholesterol deposits in cells other than those normally and physiologically rich in this lipoid substance are not a simple infiltration, but constitute an injury to the function of the cells and signify degenerative processes.

5. Pregnancy seems to furnish conditions which favor the infiltration of certain organs with cholesterol, from whatever source this may be derived. Rabbit 11, which received only 2 gm. cholesterol in 108 days by the intermittent method, and which was pregnant twice during this time, had, of all the animals, the most marked cholesterol infiltration and other pathologic conditions in the liver and kidney.

The liver of rabbits responds very readily with infiltrative processes to experimental hypercholesterolemia. This quick reaction is probably not quite analogous to anything occurring in the human liver, owing to the difference in the effect of hypercholesterolemia in herbivora and carnivora. According to Weltmann and Biach the normal elimination of cholesterol through the bile is very slight in the former but increases markedly when they are fed with this substance and the liver stores it up in large quantities. In carnivora on the other hand the normal cholesterol content of the bile is high, and doubly refractive substances are not found in the liver of the dog, the cat and the white rat, even when fed with very large quantities of food rich in

7. Abderhalden: Lehrbuch der physiologischen Chemie, Berlin, 1906, p. 592.

TABLE 1.—Cholesterol Content of Body Fluids and Various—

Number and Sex of Animals	Weight in Gm.		Kind, Periodicity and Total Number of Injections	Quantity and Concentration of Single Dose	Total Amount of Cholesterol Injected, Gm.	Duration of Experiment, Days	Quantitative Estimation of Cholesterol in Gm.			
	Beginning	End					Serum	Whole Blood	Bile	Urine
I Male	1,970	1,840	Intraperitoneal F	20 c.c. 2 to 5% unfiltered emulsions	4 in 9 days	11	*	*	*	*
II Male	1,920	1,750	Intraperitoneal F	10 c.c. 2 to 5% unfiltered emulsions	2 in 9 days	11	*	*	*	*
III Female	1,890	1,880	Intraperitoneal 1	10 c.c. 5% unfiltered emulsions	0.5	5	*	*	*	*
IV Male	1,540	1,700	Intraperitoneal 3 times a week 40	10 c.c. 2%	8	98	0.054	0.200	0.121	Not collected
V Female	1,690	1,770	Intraperitoneal 3 times a week 52	10 c.c. 2%	12.4	155	0.066	0.109	0.195	0.026
VI Female	2,200	1,960	Intraperitoneal every day 58	10 c.c. 2%	11.6	60	0.095	0.107	Numerous gallstones	Not enough obtained
VII Female	2,190	2,520	Intravenous 3 times a week 16	5 c.c. 1%	1 .	36	0.066	0.183	0.200	Not enough obtained
VIII Male	1,970	2,130	Intravenous every day 30	10 injections 5 c.c., 20 injections 10 c.c. 1%	2.5	32	.....	0.179	0.174	0.015
IX Male	1,970	1,790	13 intravenous; 10 intraperitoneal every day	Intravenously 10 c.c. 1% intraperitoneally 10 c.c. 2%	3 in 23 days	33	.....	0.320	Numerous small concretions	0.010
X Male (sick)	2,290	2,110	Intravenous every day 4	5 c.c. 1%	0.2	4	†	.....	0.041	Negative
XI Female	1,750	2,100	Intravenous by intermittent method 27	5 c.c. 1%	2 in 98 days	108	†	.....	.....	.....
XII Male	1,790	1,850	Intravenous by intermittent method 27	5 c.c. 1%	2.4 in 98 days	108	.....	0.291	Numerous small concretions	0.014

* Not examined † Died.

—Organs of Rabbits Injected with Emulsions of Cholesterol

Liver	Gallbladder	Aorta	Adrenal	Spleen	Kidney
Marked infiltration and foci of tissue destruction with cholesterol deposits. Proliferation of connective tissue	.....	Small amounts of cholesterol and fat	Enormous amounts of cholesterol	Small amount of doubly refractive substances	Small amounts of cholesterol deposits. No degenerative processes.
Marked infiltration and foci of tissue destruction with cholesterol deposits. Proliferation of connective tissue	.....	Cholesterol and fat in entire intima, which is not thickened	Fair amount of cholesterol	Negative.....	Small amount of cholesterol infiltration. Very slight degenerative processes.
Infiltration and foci of tissue destruction as in I and II, but on a small scale	.....	Negative.....	Fair amount of cholesterol	Negative.....	Limited amount of cholesterol infiltration in collecting tubules. No degenerative processes.
Moderate amount of diffuse cholesterol infiltration in peripheral portion of lobules	Negative.....	Small amount of cholesterol and fat in media and intima	Fair amount of cholesterol	Scanty amount of double refractive substances	Small amount of cholesterol infiltration. Very slight degenerative processes.
Enormous amount of diffuse cholesterol infiltration. Marked proliferation of connective tissue	A few small concretions	Small amount of cholesterol and fat in media	Fair amount of cholesterol	Fair amount of doubly refractive substances	Considerable amount of cholesterol infiltration. Slight degenerative processes.
Almost complete absence of cholesterol	Filled with small and larger gallstones	Negative.....	Moderate amount of cholesterol	Scanty amount of doubly refractive substances	Considerable amount of cholesterol infiltration. Degenerative processes more marked.
Moderate amount of cholesterol infiltration and small foci of tissue destruction with cholesterol deposits	Negative.....	Marked fatty degeneration and calcification of media (spontaneous)	Large amount in one, very scanty in other	Scanty amount of doubly refractive substances	Small amount of cholesterol infiltration. Very slight degenerative processes.
Moderate amount of cholesterol infiltration. Proliferation of connective tissue	Negative.....	Small amounts of cholesterol deposits in thickened intima	Considerable amount	Negative.....	Moderate amount of cholesterol infiltration. Slight degenerative processes.
Considerable amount of diffuse cholesterol infiltration. Slight proliferation of connective tissue	Numerous small concretions	Small amounts of cholesterol in intima	Abundance in one, scanty amount in other	Negative.....	Fair amount of cholesterol infiltration. Degenerative processes more marked.
Moderate amount of cholesterol infiltration	Negative.....	Negative.....	Moderate amount of cholesterol	Negative.....	Very limited cholesterol infiltration. No degenerative processes.
Enormous amount of diffuse cholesterol infiltration. Marked proliferation of connective tissue	Negative.....	Moderate amount of cholesterol and fat in media and intima	Small amount of cholesterol	Very scanty amount of doubly refractive substances	Very extensive cholesterol infiltration. Marked degenerative processes.
Considerable amount of diffuse cholesterol infiltration	Numerous small concretions	Negative.....	Small amount of cholesterol	Scanty amount of doubly refractive substances	Fair amount of cholesterol infiltration. Degenerative processes present.

cholesterol. (Bacmeister and Havers,[8] Weltmann,[9] Chatalow,[10] Anitschkow and Chatalow.[11]) In the omnivorous pig and in man the elimination of cholesterol by the bile is even greater than in carnivora. The liver is therefore able to adjust itself in man and in carnivora to great oscillations in the cholesterol content of the blood, whereas in herbivora, "insufficiency" on the part of this organ is, to a certain degree, physiologic (Weltmann[9]); hence the ready infiltration of the liver of rabbits in experimental cholesterolemia.

In the rabbits of my experiment this infiltration presents several peculiarities. Apparently the amount is not proportionate to the quantity of cholesterol injected, nor directly dependent on the mode of the injection. The most extensive infiltration was found in Rabbit

TABLE 2.—Cholesterol Content of Body Fluids in Normal and Control Rabbits

Number of Animal			Injections of Control Rabbits	Quantitative Estimation of Cholesterol in Gm.			
				Serum	Whole Blood	Bile	Urine
XIII	Male	Normal	.....	0.080	0.137	Trace	Negative
XVI	Male	Normal	....	0.080	0.121	Trace	Negative
XV	Male	Control	Intraperitoneal, every day; 24 injections	0.054	0.088	0.014	Negative
XVI	Male	Control	Intraperitoneal, 3 times a week for 4 months	0.030	0.106	0.024	Negative
XVII	Female	Control	Intravenous, 3 times a day, 43 days	0.052	0.130	0.038	Negative

11, which received the smallest amount of cholesterol as measured by the length of time in which it was given. In the animal similarly treated, Rabbit 12, it was very much less. Rabbit 6, which received the large quantity, 11.6 gm. of cholesterol within two months, was quite exceptional in that doubly refractive substances were almost entirely absent in the liver, while the gallbladder was filled with gallstones. Rabbit 5, having received 12.4 gm. cholesterol in five months

8. Bacmeister and Havers: Zur Physiologie und Pathologie des Cholesterinstoffwechsels, Deutsch. med. Wchnschr., 1914, xl, 385.

9. Weltmann: Zur klinischen Bedeutung des Cholesterinnachweises im Blutserum, Wien. klin. Wchnschr., 1913, xxvi, 874.

10. Chatalow: Ueber experimentelle Cholesterin-Lebercirrhose in Verbindung mit eigenen neuen Erhebungen über flüssige Kristalle des Organismus und über den Umbau der Leber, Zieglers, Beiträge, 1913, lvii, 85.

11. Anitschkow and Chatalow: Ueber experimentelle Cholesterinsteatose und ihre Bedeutung für die Entstehung einiger pathologischer Prozesse, Centralbl. f. allg. Path. u path. Anat., 1913, xxiv, 1.

by the same kind of injection, showed enormous amounts of anisotropic substances in the liver, and only a few sandy concretions in the bile. Two of the control animals had some cholesterol deposits in the liver. There is no uniformity in the distribution or in the type of the infiltration with cholesterol. In a few instances it is diffusely spread all through the lobules; in some it is located chiefly in the peripheral portion and densest nearest the periportal spaces. In general, it occurs predominantly in disseminated areas of various dimensions. These are always limited strictly to the lobules, but within these they are scattered very arbitrarily, as it seems. The cholesterol accumu-

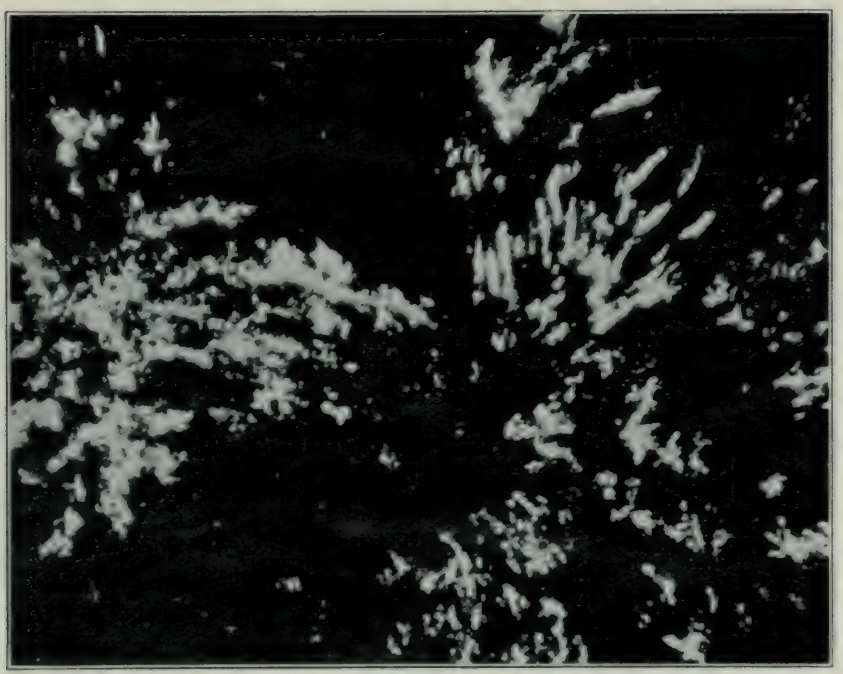


Fig. 1.—Doubly refractive substances from the liver of Rabbit 11, which received 2 gm. cholesterol by the intermittent method in 108 days. Pregnant.

lation in such areas is very marked; in the intervening portions there is none. A discriminative involvement of the liver cells or the endothelial cells cannot be observed. There is, too, an obvious radiate arrangement of the deposits (see Fig. 1); the cholesterol droplets being sometimes chiefly intralobular, sometimes chiefly in the columns of liver cells, but quite often both kinds of cells are equally involved; this is especially the case when these dense cholesterol accumulations are of small dimensions. Almost without exception the connective tissue spaces are free from cholesterol; neutral fat, however, when present, is always

found in this location. The prevalent occurrence of disseminated cholesterol deposits was not observed until the gallbladders of the rabbits were examined. On this occasion the presence of cholesterol in portions of the liver adjacent to the gallbladder in Control Rabbit 14 was discovered. In previously examined portions of the liver no doubly refractive substances had been found.

There was one type of cholesterol deposits which seemed at first limited to one group of rabbits, that is, those injected intraperitoneally with unfiltered emulsions of high concentration; but eventually identical foci, although smaller in size, were found in Rabbit 7 which had been injected intravenously with small quantities of well-filtered emulsions of 1 per cent. strength, the total amount of cholesterol being only 1 gm. in thirty-six days (see Fig. 2). These were well-demarcated areas of destruction of the liver parenchyma with large deposits of a reddish yellow material, not all of which appeared as doubly refractive substances under the polarizing microscope. The cholesterol esters were probably not simply liberated from their cell boundaries in the process of disintegration, but were broken up and new cholesterol compounds were formed which have no anisotropic properties. Since all the animals of Group 1 had such lesions and, with the one exception mentioned, none of the others, we may assume that the large quantity of cholesterol in a dose, the high concentration, and possibly the presence of large particles in the emulsion, were responsible for the destructive effect. Cells, probably perfectly normal until the time of the first injection, were suddenly taxed far beyond their capacity of intake and output, no time being given them for adaptation to an abnormal task, they succumbed completely. Rabbit 7, in which the cholesterol was gradually introduced in fine homogeneous emulsions of low strength and in small doses (1 gm. in thirty-two days), the conditions which made similar lesions possible are in all likelihood the following: (a) The rabbit was old, if we judge from the presence of the marked spontaneous arteriosclerotic processes of the aorta; (b) the liver had undergone senile changes, as shown by frozen sections not treated with alcohol; (c) the capacity of the liver cells for the taking up and giving off of an excess of cholesterol was much below par, and they succumbed under a proportionately small task and in spite of the time given them for adaptation.

Chatalow[10] attributes the injurious effect of cholesterol on the cells not to its chemical, but to its physical properties. This substance is deposited in the organs in the form of liquid crystals; as these anisotropic droplets become larger by confluence of smaller ones, and accumulate in sufficient numbers, they act as foreign bodies. But how are we to account for the accumulation of cholesterolesters in spots? Apparently only some Kupffer cells, sometimes in widely sepa-

rated regions, take up an excess of cholesterol from the blood and cause the neighboring liver cells to be loaded with anisotropic substances. The typical cholesterol infiltration seems to be focal and not diffuse, as illustrated in the liver by the disseminated areas of dense cholesterol accumulations and the focal regions of necrosis. It suggests an elective action on the part of the endothelial cells, whose normally phagocytic action is here coupled with the function of conveying their charge to other cells, that is, the liver cells.

Since to all appearances the amount of cholesterol infiltration in the liver as well as in the kidney sometimes is entirely out of propor-

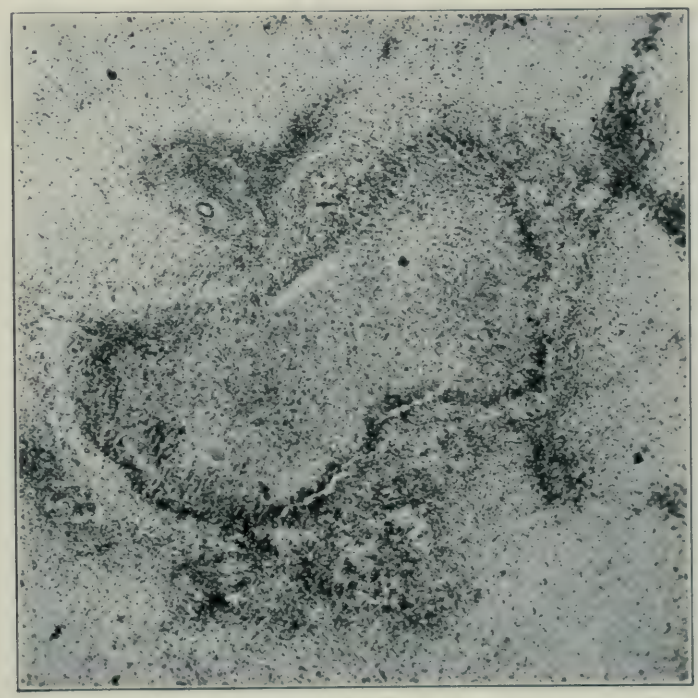


Fig. 2.—View of liver substance stained with sudan III and hematoxylin. Large focus of tissue destruction, with large amounts of cholesterol deposits, from Rabbit 1, which received intraperitoneally 4 gm. cholesterol in unfiltered emulsions of high concentration.

tion to the quantity injected, a considerable portion of it must be regarded as spontaneously produced. It may be assumed that the initial infiltration which follows the first suddenly established period of hypercholesterolemia renders the cells more susceptible to later periods and even reduces their capacity for the normal amount of work in the cholesterol metabolism. This again constitutes a factor in a general disturbance of the cholesterol regulating machinery. It has

been said that the cholesterol content of the blood is very easily changed so that even the suspending of the animal for bloodtaking produces variations in the figures. With such premises we may easily believe that the constantly repeated irritation from intraperitoneal injections for four months in a control rabbit caused a periodical occurrence of spontaneous hypercholesterolemia, followed finally by an infiltration of an organ which normally is chiefly concerned in the cholesterol metabolism, but which in the rabbit becomes readily "insufficient."

In pregnancy hypercholesterolemia occurs physiologically (Sternberg,[12] Huffmann[13]). But there is no parallel increase in the elimination of cholesterol through the bile. Bacmeister and Havers[8] attribute this hypercholesterolemia to retention of the lipoids and not to endogenous new formation in the body. Toward the end of pregnancy, the "liver filter" becomes denser and the liver cells shut off the outflow of the blood cholesterol into the bile. These authors admit, however, that there may be also an alteration in the constitution of the lipoids themselves, as a result of which the chemically changed cholesterol compounds cannot pass through the unchanged liver cells. A normal pregnant rabbit which I examined showed no trace of anisotropic substances in sections from various portions of the liver, but I found a fair amount of cholesterol in that of the pregnant Control Rabbit 13, which received sixteen intravenous injections of the control fluid (free from cholesterol) and was under observation for forty-three days. A pus infection in the external meatus which had been present was discovered only when the badly involved ear was to be used. It was also bitten in the ear by another rabbit and had to be isolated. It is reasonable to assume that the repeated irritation from intravenous injections, the treating of a painful ear and even the frequent examination of the rectal temperature contributed toward further increasing the physiological hypercholesterolemia of pregnancy with subsequent cholesterol infiltration in the liver. Rabbit 11, which was injected intravenously by the intermittent method and received only 2 gm. in one hundred and eight days, had, of all the animals, the most marked cholesterol infiltration of the liver and the kidney. It was pregnant twice during this period and in that condition at the time of death. There is no doubt that a large part of the amount of cholesterol in the organs of this rabbit was not that retained from the injections but was spontaneously produced. We have here an example, I believe, of a case in which hypercholesterolemia and cholesteatosis may be the cause and effect

12. Sternberg: Die Nebenniere bei physiologischer (Schwangerschaft) und artifizieller Hypercholesterinämie, Beitr. z. path. Anat. u. z. allg. Path., 1914, lx, 91.

13. Huffmann: Zur Bestimmung des Gesamtcholesterins im Blute an geburtshilflichen und gynäkologischen Fällen, Zentralbl. f. Gynäk., 1915, xxix, 33.

of pathologic conditions. The primary cause of both may be disturbed cellular functions of momentary, short or long duration, thereby changing the lipoid character of the cell. Food as such probably plays a very small part, if any, in the production of cholesterol deposits in functionating organs.

An interesting coincidence is the lack of any noteworthy cholesterol infiltration of the liver and the presence of numerous gallstones in the gallbladder of Rabbit 6 which was injected intraperitoneally each day for two months with 10 c.c. of a 2 per cent. emulsion. The kidney showed as much cholesterol infiltration as in other marked cases. The

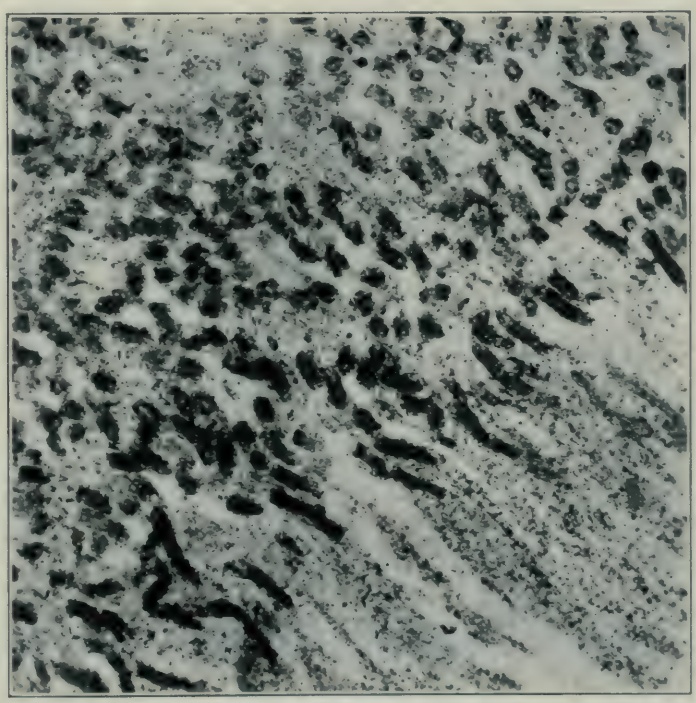


Fig. 3.—View of kidney tissue stained with sudan III. Marked infiltration of tubules with cholesterol, from Rabbit 11.

cells of this liver were apparently unusually permeable and capable of taking up and giving off large quantities of cholesterol without loading themselves with anisotropic substances. It was an exceptionally well functionating filter and in this respect more comparable to the liver of carnivora: but on account of the unhindered passage of enormous quantities of cholesterol through the rabbit's liver, there was a constant abnormally high cholesterol content of the bile and gallstones formed. In two other rabbits, which had numerous sandy concretions, the infil-

tration of the liver was considerable, although not excessive, and was of the diffuse type involving chiefly the Kupffer and endothelial cells.

The results of my experiments differ in some respects from those of Chatalow.[10] These differences arise, of course, from the methods employed. In his case considerable quantities of fat were given with cholesterol and consequently large amounts of fat reappeared in the liver. In my experiments no fat and no other lipoids besides cholesterol were given, and in no instance does fat appear in the liver structure; where it does occur, it is limited to the periportal spaces widened by proliferation of connective tissue. Chatalow's explanation of the manner in which the anisotropic infiltration or "Verfettung" may occur is not applicable to my observations. He states that "it is necessary that isotropic fats accumulate in sufficient quantity in the organ and perhaps also that free fatty acids develop, in order that cholesterol may be bound and retained." According to him, deposits of anisotropic fats are observed chiefly in those portions of the liver in which the isotropic fats are concentrated, and consequently also saturated with cholesterol compounds. Chatalow himself admits that in his explanation he considers exclusively his experiments of feeding animals with cholesterol dissolved in sunflower seed oil. That in some pathologic conditions of the human liver the increase of the fatty constituents may be associated with an increase of its cholesterol content and with a corresponding rise in the cholesterol content of the bile, appears from the work of Le Count and Long.[14] I also failed to find proliferation of the epithelium of the bile ducts or hypertrophic proliferation of these ducts such as Chatalow describes. Anisotropic substances were not found in the epithelium of these ducts or in that of the gallbladder, and only rarely a substance which takes the cholesterol tint with sudan III was seen in the epithelial cells of the smaller bile ducts. Chatalow states that the oil of sunflower seed does not produce any pathologic alterations in the liver, that it appears very soon in the epithelial cells of the bile ducts and in the liver cells surrounding the central vein, and that it is eliminated with the bile, passes over into the blood, and in continued feeding produces a diffuse, even infiltration in the liver. He believes that the presence of fat in the epithelial cells favors the increased elimination of cholesterol compounds and that the irritation from these incites the proliferation of connective tissue. Finally a substitution of true liver cells by proliferated cells of the bile ducts, as he observed could not be demonstrated in the livers of my rabbits. Whenever the infiltration with cholesterol was diffuse and located in the peripheral portion of the lobule, the cells thus infiltrated reached

14. LeCount and Long: The Relation Between the Fat Content of the Bile and Fatty Changes in the Liver, Jour. Exper. Med., 1914, xix, 234.

to the very border line, while the newly formed cells observed by Chatalow, although morphologically like true liver cells, did not functionate as such, that is, they did not take up cholesterol. In closer analogy with my findings are the observations of Rothschild,[15] who studied the relations of hypercholesterolemia in rabbits following bilateral suprarenectomy, and the increase of the amount of cholesterol in the liver and in the bile. Deposits of anisotropic substances were found

Fig. 4.—View from the same kidney as Figure 3. Paraffin section stained with hematoxylin and eosin. Triangular area with the base toward the capsule showing marked degenerative processes.

only in Kupffer cells. The epithelial cells of the bile ducts were free from cholesterol, and those of the gallbladder only occasionally contained single isotropic fat droplets. According to Rothschild the Kupffer cells are the intermediary and the liver the "regulating" organ

15. Rothschild: Ueber die Beziehungen der Leber zum Cholesterinstoffwechsel, Beitr. z. path. Anat. u. z. allg. Path., 1914, lx, 66.

in the cholesterol metabolism, inasmuch as it maintains the cholesterol equilibrium of the organism through the elimination in the bile.

The sources of the cholesterol in spontaneous hypercholesterolemia, physiological and pathological, are yet unknown. They are probably manifold, including physical and chemical alterations of the cell as well as functional disturbance of entire organs. The various parts of an intricate cholesterol metabolic apparatus may be in such intimate interaction that insufficiency on the part of one will throw an extra burden on another engaged in a different manner in the cholesterol work, which again involves another, producing a state of functional instability. Some organs seem to be preeminently depots, such as the adrenals, the ovaries,[6] the fatty tissue, from which the cholesterol is mobilized, so to speak, in time of general disturbance. Rothschild[16] showed that in a state of inanition rabbits present a condition similar to that following suprarenectomy, namely, an increase of cholesterol in the blood, the adrenal, the liver and the bile. He believes that the increase of this substance in some of the vital organs may be attributed to an increase of the blood cholesterol, and this again to a greater activity in the catabolic cellular processes, chiefly in the less vital organs (fatty tissue). The great variations in the effect of cholesterol on the liver of the rabbits in my experiments indicate a great variability in the functional adaptability of the liver cells to the increased influx of cholesterol from the blood. Such differences may arise from age, sex, disposition, that is, individual tendencies, transitory or lasting morbid conditions. Cholesterol alone in excessive quantities may have a destructive effect on normal, healthy cells and injure them beyond the possibility of recuperation. Continued overtaxing of the cells from long-sustained hypercholesterolemia may cause "insufficiency" with ultimate destruction of parenchyma. Individually, the normal function may be below the average requirements and this relative insufficiency may cause deposits in other organs; but the cells, primarily weakened and impaired, succumb readily even to a slight increase of the blood cholesterol. This primary alteration itself may be an alteration of the lipoid character of the cell. According to Chvostek,[17] the infiltration of an organ with cholesterol is preceded by an alteration in the constitution of the cells (cutaneous), as a result of which the lipoid substances already existing in the cells, are separated from their combinations and made visible, and the introduction of fresh cholesterol causes an infiltration of such cells with this substance.

16. Rothschild: Zur Physiologie des Cholesterinstoffwechsels. V. Der Cholesteringehalt des Blutes und einiger Organe im Hungerzustand, Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 227.

17. Quoted from Weltmann and Biach (Note 6).

The mucosa of the gallbladder examined by the polarizing microscope was absolutely free from doubly refractive substances in all rabbits. In histological sections three of them, Rabbits 6, 8 and 9, presented an exceptional feature. A substance which stains reddish with sudan III and purplish blue with Nile blue sulphate is present abundantly in a number of villi. It is not in the epithelium, for this is shed, but it generally occupies the central portion of the villus, forming designs which recall the chyle ducts in the intestine. They are often branched or spider like and are probably widely distended lymph channels filled with fat and such cholesterol compounds as have no anisotropic properties (see Fig. 5). In the finer branches particularly

Fig. 5.—Gallbladder, stained with sudan III and hematoxylin. Widely distended lymph vessels in the mucosa filled with cholesterol and fat, from Rabbit 8, which received intravenously 2.5 gm. cholesterol in thirty-two days.

it is clearly seen that rather large cells, which occupy these vessels, are loaded with granular reddish stained material. Kaufmann[18] mentions such observations with regard to the human gallbladder; the substance, which is within large cells in lymph vessels, is fat, and he believes that it is resorbed from the bile. Lichtwitz[19] describes masses

18. Kaufmann: Lehrbuch der speziellen pathologischen Anatomie, Berlin, 1911 (1), p. 622.

19. Lichtwitz: Ueber die Bildung der Harn- und Gallensteine, Berlin, 1914, p. 69.

lying beneath the epithelium in a human gallbladder, which were doubly refractive substances. He states that in some places they had broken through the mucosa. A relation to the lymph vessels could not be observed. From the picture he concludes that the masses containing cholesterol penetrate from the gallbladder to the surface of the mucosa, thence into the bile. According to him the bile receives its cholesterol from two sources; from the liver cells and from the gallbladder wall. He writes: "Since the solubility of cholesterol is achieved by means of other colloidal substances, it is quite possible that the condition of the solution varies with the source of the cholesterol." The "liver cholesterol" may have a solubility different from that of the "wall cholesterol." In this interpretation he disagrees with Aschoff and Bacmeister[20] who believe that the cholesterol of the gallbladder wall has been resorbed from the bile as esters and set free in the epithelium of the bladder. The diverging views about the origin of the biliary cholesterol are represented on the one side by Chauffard, Laroche and Grigaut,[21] and Naunyn[22] who consider it as a secretion of the epithelial cells of the bile ducts, and on the other side by Aschoff,[23] Landau and McNee[24] and Rothschild.[15] According to these authors, cholesterol found in the epithelium of the gallbladder is a result of resorption from the bile.

In several rabbits the mucosa of the gallbladder showed a very extensive desquamation of the epithelial cells, which for various reasons I am inclined to consider as due not to postmortem changes, but to the irritating intravitam action of an excess of cholesterol in the bile. The necropsy was made immediately after killing the animals, and the bile was withdrawn with a pipet. In Rabbit 11, which died unexpectedly and whose necropsy could be made only on the following day, the mucosal lining was preserved. It was intact also in Rabbit 12. These two rabbits received very small quantities of cholesterol by the intermittent method during a period of 108 days. From the extensive cholesterol infiltration in the liver we may presume that the elimination of cholesterol through the bile was not abnormally increased. In all those rabbits which had gallstones or small concretions, besides some which had none, but whose bile probably had an excess of cholesterol, the desquamation of epithelial cells was very marked. The shed cells

20. Quoted from Lichtwitz (Note 19).

21. Chauffard, Laroche and Grigaut: Sur l'origine de la cholestérine biliaire. Recherches expérimentales sur la cholestérinémie après ligature du cholédoque. Soc. biol., 1913, lxxiv, 1005 and 1093.

22. Naunyn: Quoted from Lichtwitz (Note 19).

23. Aschoff: Zur Frage der Cholesterinbildung in der Gallenblase. München. med. Wchnschr., 1906, liii, 1846.

24. McNee: Zur Physiologie des Cholesterinstoffwechsels, Beitr. z. path. Anat. u. z. allg. Path., 1914, lviii, 667.

retained in the lumen in paraffin sections, showed all stages of disintegration. The denuded villi were sometimes matted together forming a network in the meshes of which there were cell debris and pigment.

Gallstones of any appreciable size produced by experimental hypercholesterolemia have not been reported previously in literature. The contracted and knotty gallbladder of Rabbit 6 contained a number of small concretions and twelve stones with a diameter of 2 and 3 mm.; the small amount of bile which could be withdrawn was full of black granules. The gallstones were irregular, brittle and not faceted. Some of them were treated and embedded in paraffin by the method of Aoyama.[24] Sections stained with methylene blue showed that disintegrated cells formed the framework of these stones, while cell remnants and faint nuclei were still discernible in the outer portion of such sections. The cell debris was rolled up and held together with pigment and calcareous substances and the masses thus formed were placed tile-like in apposition forming parallel trabeculae. Bacteria were not found in the gallstones, in the lumen or in the gallbladder wall. All indications of inflammatory processes also were lacking. Evidently these gallstones were formed in sterile bile. The liver of this rabbit did not show any noteworthy cholesterol infiltration in sections taken from five different portions. The greatly hypercholesterolemic blood passed through this exceptionally permeable organ unimpeded and enormous quantities of cholesterol were poured out into the bile, which acted as a violent irritant on the epithelial cells; they were injured and desquamated en masse, clumped together and formed the organic scaffold to which the substances precipitated from the bile were anchored. These multiple stones of trabecular construction with a clearly organic scaffold, of recent formation and of a noninflammatory origin I do not venture to identify with types of human gallstones. The differences in the normal conditions in rabbits from those in man suggest equal differences in pathologic processes. It is known that human gallstones not soluble in human bile may dissolve in animal bile. Aschoff[25] pointed out that not only is the cholesterol content of the bile in the dog, the rabbit and the ox strikingly small as compared with that in man, but there are also differences in the relative values of the other constituents, all of which result in a difference of solubility.

The chief analogy of value between these experimentally produced gallstones and those occurring in man lies in the association of gallstone formation with hypercholesterolemia. The frequent occurrence of gallstones in women has often been attributed to mechanical factors,

25. Aoyama: Zur Frage der Cholelithiasis, Beitr. z. path. Anat. u. z. allg. Path., 1913, lvii, 169.

26. Aschoff: Wie entstehen die reinen Cholesterinsteine? München. med. Wchnschr., 1913, lx, 1753.

among them pressure effects in pregnancy. Hypercholesterolemia is always associated with this condition, and probably plays the greater part. Herrmann and Neumann[27] believe that the high cholesterol content of the blood in pregnancy is the result of retention in the blood; in the puerperium most of it is eliminated by the milk; nonlactating women retain the lipoidemia longer. Aschoff,[25] however, states that only part of the blood cholesterol is carried off by the milk, as also by the urine; another portion is eliminated through the bile, as some observations of McNee[28] indicate. According to Bacmeister and Havers,[8] the greater density of the liver during the latter part of pregnancy causes retention of the blood cholesterol, and immediately after delivery cholesterol is suddenly poured out in abundance into the bile. Aschoff[29] calls attention to the observation that the first attacks of gallstones are often observed in pregnancy and that we may assume stone formation to occur during or shortly after labor. The structure of these pure cholesterol stones, which are not concentric, but of a chaotic, trabecular type, indicates a more or less hurried formation by the crystallizing out of pure cholesterol from the bile. They are, as a rule, of a noninflammatory origin, occur at a relatively early age, and are the result of hypercholesterolemia followed by sudden precipitation processes in the bile under the influence of labor or the puerperium.

Compared with the well marked effects of cholesterol in the kidney and liver in most of the rabbits the involvement of the aorta was slight. Macroscopic changes were absent in all but one. As examined by the micropolariscope, cholesterol was entirely absent in three, and the amount was slight in three others. The very marked process of degeneration in the media of Rabbit 7 must be considered as spontaneous, that is, of the adrenalin type referred to in literature, because none of the alterations were found in the aorta of any of the others, all of which, except one, had received much larger doses. Weltmann and Biach[6] state that they failed to produce any atheromatous changes with deposits of doubly refractive substances in the aorta of rabbits fed with cholesterol for some time. By primarily injuring the blood vessels through injections of adrenalin an arteriosclerosis of the adrenalin type occurred in such rabbits. Anisotropic substances, however, were not observed by them. Perhaps much larger quantities of cholesterol by feeding than these authors used and larger amounts than I administered by intraperitoneal and intravenous injections are necessary to

27. Herrmann and Neumann: Ueber die Lipoide der Gravidität und deren Ausscheidung nach vollendeter Schwangerschaft, Wien. klin. Wchnschr., 1912, xxv, 1557.

28. McNee: Zur Frage des Cholesteringehalts der Galle während der Schwangerschaft, Deutsch. med. Wchnschr., 1913, xxxix, 995.

29. Aschoff: Bemerkungen zur Arbeit von McNee, Deutsch. med. Wchnschr., 1913, xxxix, 995.

produce such thickening of the intima with large cholesterol deposits as Anitschkow[30] described. In my observation large intima cells were present in nearly all the instances where cells of this layer of the vessel wall were infiltrated with cholesterol; but they were not increased in number; they were simply enlarged intima cells proper, the ballooned protoplasmic body bulging out into the lumen of the vessel. Nodular thickening of the intima occurred in two cases, but it was of the type of hypertrophic connective tissue, in the center of which there were some cholesterol deposits. Fat was generally found in addition to cholesterol and often in greater amount than this. An observation of some interest was the uniform marked infiltration with fat and cholesterol of the entire intima and some adjoining layers of the media in an instance where a tear through the inner layers of the aorta was found (probably agonal or postagonal).

As to the adrenal, it is impossible to systematize the observations. Seemingly there is no correlation between the amount of cholesterol in this organ and that in the liver and kidney as far as these experiments are concerned. As determined by the micropolariscope, it varied sometimes greatly in the two adrenals of the same rabbit. In Rabbit 14, a control animal for intraperitoneal injections, the amount of cholesterol in both adrenals was scanty, in Rabbit 13, control animal for intravenous injections, which was pregnant when killed, there was an abundance. The same was observed in a normal pregnant rabbit. Rabbit 11, also pregnant at the time of death, and in which the cholesterol infiltration in the liver and kidney was most marked, had a small amount of cholesterol in the adrenal. In still another control animal in the early stage of pregnancy there was a very scanty amount of doubly refractive substance in the adrenal. There were great variations in the state of division and in the distribution of the crystalline substances. They were finely or very finely divided or occurred in coarse conglomerations. In four cases the glomerulosa was almost entirely free from cholesterol. Fat was present in abundance in all, and apparently more so in proportion as the amount of cholesterol was scanty.

My observation of the amount of doubly refractive substances in the spleen of the cholesterolized rabbits agrees with that of Weltmann and Viach, who found only small quantities of anisotropic droplets in this organ. There was no cholesterol, as determined by the polarizing microscope, in the spleen of four, and a very scanty amount in that of six rabbits. In all it occurred in exceedingly finely divided crystalline substances. But as in the kidney and the gallbladder, so also in

30. Anitschkow: Ueber die Veränderungen der Kaninchenaorta bei experimenteller Cholesterinsteatose, Beitr. z. path. Anat. u. z. allg. Path., 1913, lvi, 379.

the spleen, there may have been cholesterol compounds which were not anisotropic; for in sections stained with sudan III there were often more or less numerous small areas which took the typical cholesterol tint. A striking occurrence of large infiltrated cells, such as described by Anitschkow[31] and by Soper,[32] I was unable to observe.

Weltmann and Biach[6] are the only authors, to my knowledge, who have produced an infiltration of the kidney with cholesterol in rabbits. In addition to feeding them with this substance they injected uranium nitrate and adrenalin in order to favor such an infiltration, which they failed to produce with cholesterol alone. They fed a rabbit for twenty-four days with 1 gm. cholesterol daily. During the last seven days of this period uranium nitrate was injected intraperitoneally in three doses. Macroscopically the kidney showed the signs of nephritis. The polarizing microscope revealed doubly refractive substances in the epithelium of the tubules which appeared as "light stripes." "This localization," the authors write, "is interesting, inasmuch as in nephritis from uranium poisoning an injury to the tubular apparatus is, according to the investigations of Suzuki, the chief involvement." A second experiment, in which the effect of uranium nitrate was combined with that of adrenalin, the kidney showed a similar picture, although less pronounced. A control experiment with pure uranium nitrate without cholesterol had negative results.

The results of the polariscopic examination of the kidneys in my experiments need a special explanation. Doubly refractive droplets, which after heating show the cross figure on cooling, could be demonstrated only in one case, where these substances formed luminous, compact bands of varying length within the lumen of the straight tubules, and formed a narrow lining of some neighboring tubules. Single scattered droplets were seen in many kidneys in considerable number as they were quite generally observed in the spleen. But the substance which infiltrates tubules in foci, and which takes the typical yellowish red tint with sudan III, did not flash up as sparkling doubly refractive droplets under the polarizing microscope. They appeared as tubules with a somewhat dull silvery hue. Their relief against the background with darker tubules was not marked enough to give satisfactory photomicrographs. But so invariably did they reappear in sudan III stained sections that the conviction was very strong that this substance was cholesterol. It would be interesting to know whether Weltmann and Biach's remark that the doubly refractive droplets "als

31. Anitschkow: Ueber experimentell erzeugte Ablagerungen von anisotropen Lipoidsubstanzen in der Milz und im Knochenmark, Beitr. z. path. Anat. u. z. allg. Path., 1913, 57, 201.

32. Soper: Zur Physiologie des Cholesterinstoffwechsels. VI. Ueber Beziehungen der Milz zum Cholesterinstoffwechsel, Beitr. z. path. Anat. u. z. allg. Path., 1915, lx, 232.

helle Streifen aufleuchteten" would apply to the tubules which I describe as silvery. The kidneys examined had been in formalin for periods of different lengths. The characteristic cross figure could not be observed.

Several explanations for the nature and aspect of these substances are possible. The doubly refractive droplets are advantageously studied when isolated. This is easily done by allowing them to pass with the water beyond the margin of the section, or by squeezing them with slight pressure out of a well-infiltrated section, for example, from a fresh adrenal. It will then be noticed that the droplets are of all sizes and that the black cross is still discernible in extremely minute droplets, so minute that they cease to sparkle, and droplets can be seen so infinitesimal that the cross figure is beyond the limit of vision. There is no reason to believe that in a collection of droplets in which all those large enough to exhibit the cross can be identified as anisotropic droplets the smallest ones are different. Droplets of such extremely small dimensions would hardly flash up with brilliancy, but would rather have a dim appearance under the polarizing microscope. Weltmann and Biach say of the adrenals of normal rabbits, that "they show a fine fog of doubly refractive droplets and relatively few large ones." "Fine fog" is the best description of such a picture as I have observed in portions of adrenals from cholesterolized rabbits and it is not unlike the appearance of tubules of the kidneys infiltrated with cholesterol. In sections of the liver, in which the anisotropic infiltration appeared in compact radial sparkling columns, these often stopped abruptly, but it could be seen that sometimes beyond such heavily infiltrated liver cells there were in the same columns stray masses of presumably the identical substance, but so scanty in amount that they appeared only as dull silvery shreds. With the high power lens the orange red substance in the infiltrated tubules appeared as extremely fine granules; such tubules looked as if powdered. This was an average appearance. However, in a few cases, particularly in Rabbit 11, there were larger granules in addition to this dustlike substance and we might conclude that these were the typical cholesterol esters. They were not neutral fat; even if large they never had the even contour or the red color of the fat droplets. Yet they did not flash up as anisotropic droplets under the micropolariscope. We must therefore conclude that these were cholesterol compounds which are not anisotropic. I have convinced myself that the cholesterol esters, which appear as doubly refractive substances, are not all identical in their characteristics. At least there are variations when the tissues have been fixed in formalin. The melting point is not the same; in fact there is quite a range of temperature within which these substances may melt; on cooling they do not all reappear as droplets with the cross figure, an observation

which is also made with fresh sections. Their behavior toward stains is not invariably the same. Incidentally, I made the observation that in some sections of the aorta the cholesterol esters had resisted both the sudan III and the hematoxylin stain and retained their anisotropic properties unimpaired. We may have in the kidneys of the cholesterolized rabbits a variety of cholesterol esters. There were droplets of extremely small size, and others which had no anisotropic properties.

In some urines freshly examined doubly refractive droplets were found, and in some appreciable amounts of cholesterol could be estimated with the colorimetric method.

Practically all the rabbits injected with cholesterol showed some degree of infiltration with this substance in the kidney. In the control animals none was found. The type of cholesterol infiltration was the same in all rabbits, and in no instance was there a general involvement of the tubules; it was pre-eminently localized. Single tubules or a varying number of them were thus marked out from the rest. The subcapsular zone frequently had a marbled appearance due to this singling out of tubules by the stain characteristic of cholesterol. The convoluted tubules in the immediate neighborhood of the glomeruli were often affected, though the infiltration was not limited to this type of tubule. In some cases only those in the labyrinths were involved, but quite often also the tubules in the medullary rays were stained orange red. An infiltration of the lower portions of the collecting tubules and of Bellini's ducts was not observed. As a rule, the glomerular tufts did not show any noteworthy cholesterol deposit. In Rabbit 11, however, they were heavily involved and correspondingly short silvery bands and curved lines were seen in a great many of them with the polarizing microscope. Degenerative processes were present in the majority of the kidneys, but in several of them they were slight. Among them changes in the glomeruli did not play a prominent part. Vacuolization, disintegration and desquamation of epithelial cells and atrophy of tubules were the chief processes; round cell infiltration and proliferation of connective tissue constricting tubules also occurred. Cholesterol deposits were not only seen in apparently well-preserved or swollen epithelial cells, but also in atrophied tubules. In some cases the extent of the infiltration and the degenerative processes were apparently not in proportion to the amount of cholesterol injected and individual and additional physiologic and pathologic influences would seem to have played a part. The most pronounced alterations were in a rabbit which had been injected by the intermittent method with only 2 gm. in 108 days (see Figs. 3 and 4). In Rabbit 12, similarly treated, the cholesterol infiltration was less extensive and the degenerative processes much less marked. One is inclined to believe that the irritation which follows even very small doses is of long duration, and that

the infiltration remains and lowers the resistance to later irritating excesses of cholesterol in the blood. "Insufficiency" of the cells is brought about not by a sudden overpowering onrush of cholesterol, but by a slow, insidious, vitiating irritation. It would seem that the source of danger lies not in the quantity of the blood cholesterol, but in the mere existence of deposits of this substance in the cells. The infiltrated cell is already pathologic or on the verge of becoming so and offers less and less resistance to a periodical hypercholesterolemia. This rabbit was pregnant twice during the period of the experiment. It will be of interest to discover whether the nephritis which not so infrequently accompanies pregnancy is associated with a marked increase of the cholesterol content of the kidney.

Since Weltmann and Biach failed to obtain a cholesterol infiltration in the kidney of rabbits by feeding them this substance, but succeeded in producing it by injecting uranium nitrate and at the same time feeding cholesterol, it is likely that the quantity of cholesterol given by feeding was not sufficient to bring about such a state of hypercholesterolemia as I produced and maintained by direct injections into the circulation of relatively very small amounts of cholesterol. These authors reported as a "striking fact" that a body which passes into the serum of herbivora cannot be eliminated. In rabbits they found a progressive rise in the cholesterol curve, which even after ten days of cessation of feeding did not show any tendency to fall. We may then suppose that the rabbits which were fed for sixteen days with 1 gm. cholesterol daily constantly accumulated this substance in the blood, but still did not produce an infiltration of the tubular epithelium of the kidneys. When uranium nitrate was injected, these cells were injured and from that time no resistance was offered to the entrance of the excess of the blood cholesterol. What was achieved here by uranium nitrate is probably brought about by a variety of morbid conditions, all of which tend to lower the vitality or possibly change the lipoid character of the cells. An illustration of this we have in Rabbit 10, which was ill and whose urine was dark and thick before the injections were given. Of these injections only three could have had an effect; the animal died immediately after the fourth and the autopsy was made at once, hence only 125 mg. of chesterol had passed into the blood. In the kidney a small number of convoluted tubules were infiltrated with cholesterol in a manner like that observed in the other rabbits. These cells were preliminarily injured and prepared for a ready infiltration.

The urine was collected from the urinary bladder at the necropsies and specimens examined under the micropolariscope; in the majority of cases doubly refractive substances were observed. Whenever the

quantity of urine was sufficient the cholesterol content was determined by the colorimetric method. The figures given in the table are probably a little lower than they should be, because some of the sediment was used for microscopic examination. Epithelial cells were found in only a few cases and always in small numbers; casts were observed in only one instance. In several rabbits the urine was very thick and creamy.

Hypercholesterolemia occurs regularly in chronic nephritis, according to Weltmann,[9] Bacmeister and Henes,[33] Chauffard, Laroche and Grigaut,[34] Widal, Weill and Laudat.[35] Weltmann could not demonstrate an obviously constant dependence of the serum cholesterol on the gravity of the renal disturbances, while Bacmeister and Henes believe that it runs parallel with the degree of the generally impaired condition of health. Amyloid kidney is also associated with an increase of the blood cholesterol. Doubly refractive substances have been found in the sediment of the urine in chronic nephritis and in amyloid kidney by Lavrinovich[36] and Secchi.[37] There is no constant relation between the cholesterol content of the urine and blood, according to Ferré, Mauriac and Defaye.[38] Quantitative analyses of the kidneys for their content in fat and fatlike substances have not had uniform results (Thaissen and Hess,[39] Rosenfeld,[40] Orgler[41]), Löhlein[42] bases his strict distinction between "fat infiltration" and "fatty degeneration" on the pathologic and clinical differences. In the former, droplets consisting

33. Bacmeister and Henes: Untersuchungen über den Cholesteringehalt des menschlichen Blutes bei verschiedenen inneren Krankheiten, Deutsch. med. Wchnschr., 1913, xxxix, 544.

34. Grigaut: Dosage comparé de la cholestérine dans le serum et dans les oedèmes, Compt rend. Soc. de biol., 1911, lxx, 317.

35. Weill and Laudat: Etude comparative du taux de la cholestérine libre et de ses èthers dans le serum sanguin, Soc. de biol., Compt. rend. hebd. d. sc. et mem., 1913, lxxiv, 882.

36. Lavrinovich: Cholesterin Esters in the Urine, Jour. Am. Med. Assn., 1914, lxiii, 1615; abstract from the original article in Russk. Vrach., 1914, xiii, 19.

37. Secchi: Sul valore clinico dei lipoidi birifrangenti nell urina, Bull. Sc. Med., 1914, p. 83.

38. Ferré, Mauriac and Defaye: Sur la quantité de cholestérine contenue dans certains liquides normaux ou pathologiques de l'organisme, Compt. rend. Soc. de biol., 1912, lxxiii, 141.

39. Thaissen and Hess: Beiträge zur physiologischen Chemie des Cholesterins und der Cholesterinester, Biochem. Ztschr., 1914, lxii, 89 and 115.

40. Rosenfeld: Ueber Organverfettung, Verh. d. 20, Kongr. f. inn. Med., 1902, 235.

41. Orgler: Ueber Beziehungen zwischen chemischem und morphologischem Verhalten pathologisch veränderter Nieren, Verhandl. d. deutsch path. Gesellsch., 1903, vi, 76. Chemische Niereuntersuchungen unter Berücksichtigung des histologischen Bildes, Virch. Arch. f. path. Anat., 1904, clxxvi, 413.

42. Ueber die in pathologisch veränderten Nieren sichtbar werdende fettähnliche Substanz, Verhandl. d. deutsch. path. Gesellsch., 1904, viii, 33. Ueber Fettinfiltration und fettige Degeneration der Niere des Menschen, Virch. Arch. f. path. Anat., 1905, cviii, 1.

exclusively of "fat" are accumulated in the epithelial cells of the tubules, involving either the entire parenchyma or such portions as are morphologically connected. The infiltrated cells are not injured, and albuminuria is not an associated feature in this condition. "Fatty degeneration," on the other hand, is characterized by focal deposits of highly refractive substances in the parenchyma, especially in the cortex. The epithelial cells are gravely damaged, and fat and fatlike substances occupy the intertubular tissue. Clinically, albuminuria is generally observed. This fatlike substance found in the kidney in pathologic conditions was at first considered as "protagon" (Stoerk,[43] Orgler,[44] Löhlein[42]), however, Panzer[45] reported that procedures applicable to the demonstration of protagon proved to be of no avail with kidneys morphologically rich in doubly refractive substances, while with proper measures for the extraction of this lipoid, cholesterol and cholesterolesters were obtained. Several large white kidneys were thus analyzed.

The cholesterol infiltration of the kidneys of rabbits apparently resembles certain pathologic conditions in the human kidney, such as the large white kidney. This fact is of value, as we have to take into account that an infiltration of the liver such as occurs in rabbits is scarcely analogous to processes of the liver in man. How can we conceive of a spontaneously produced cholesterol infiltration in the human kidney? It is likely that the maintenance of the cholesterol equilibrium is dependent on the interaction of the various components of a regulating apparatus, the composition and the exact working of which we do not yet know. Derived from the food, as seems to be established, cholesterol forms a constituent of the cells of all the tissues and is present in all the normal and pathologic fluids of the body. It is stored in some organs and tissues, which seem to be cholesterol depots, such as the adrenal, the ovary and the adipose tissue. The close relationship, embryologically, between the kidney, the adrenal and the ovary may account for the relatively high normal cholesterol content of the kidney and the ready infiltration with this substance in pathologic conditions. The normal cholesterol content of the blood remains the same within certain limits. It rises and falls according to physiologic and pathologic conditions, which, apart from any transitory hypercholesterolemia following a diet rich in cholesterol, is probably entirely independent of food as hypercholesterolemia occurs

43. Ueber Protagon und über die grosse weisse Niere, Sitzungsb. d. k. Akad. d. Wissensch., Math.-naturw. Klasse, Wien., 1905, cxv, 31.

45. Panzer: Ueber das sagenannte Protagon der Niere, Ztschr. f. physiol. Chem., 1905, xlviii, 519. Doppeltbrechende Substanzen aus pathologischen Organen, Ibid., 1907, liv, 239.

in inanition (Rothschild,[16] Terroine,[46] Mayer and Schaeffer,[47] Ellis and Gardner[48]). The causes of such increase of the blood cholesterol are presumably manifold, but the processes may be chiefly that cholesterol is mobilized from depots and is also liberated from cells of functionating organs by metabolic and catabolic processes in physiologic conditions. Physical as well as chemical factors may be at work. In a measure, as these oscillations in the cholesterol content of the blood occur and reoccur and pathologic conditions exist to retard and hinder the exact working of the entire machinery, cholesteral may be taken up more readily than under normal conditions, by cells which have been bathed in and irritated by hypercholesterolemic blood. The causes which lead to the development of a large white kidney and to the development of the nephritis of pregnancy, may be those which produce a frequent hypercholesterolemia; cause and effect may here be in reciprocal interaction. In morbid conditions from many causes, there is probably a more or less prolonged instability of the cholesterol equilibrium, and insufficiency of one component ordinarily concerned chiefly in the regulation of the equilibrium, as the liver is supposed to be, throws greater demands on other organs which are physiologically less prepared for such work; if in addition the cells are debilitated, they will soon be incapacitated and cholesterol will not be disposed of to an extent proportionate to the requirements, but will be deposited in excess and will act with destruction like a foreign body.

SUMMARY

In experimental hypercholesterolemia the effects vary, not only according to the kind, size, and number of the doses, but also greatly according to the general condition of the rabbit, individual as well as physiological and pathological. The amount of cholesterol seems less essential than the degree of constitutional integrity and functional activity of the cell which prevails prior to the injection, or which results from the first establishment of an experimental hypercholesterolemia.

The ready infiltration in the liver of the rabbit, in contrast to that of carnivora, is an expression of insufficiency on the part of an organ which has normally a light task to perform in the cholesterol metabolism.

46. Terroine: Nouvelles recherches sur l'influence de l'inanition et de la suralimentation sur la teneur des tissues en substances grasses et en cholestérine, Jour. de physiol. et de path. gén., 1914, xvi, 408.

47. Mayer and Schaeffer: Variations de la teneur des tissues en lipoides et en eau au cours de l'inanition absolue. Activité physiologique des tissues, Jour. de physiol. et de path. gén., 1914, xvi, 203 and 244.

48. Gardner: The origin and testing of cholesterol in the animal organism, IX. On the cholesterol content of the tissues, other than liver, of rabbits under various diets and during inanition, Proc. Roy. Med. and Chir. Soc., 1912, lxxxv, 385.

As a result of hypercholesterolemia gallstones may be formed in sterile bile without infection or injury of the gallbladder. Their formation is preceded by desquamation of the epithelial cells, due to the irritating action of an excess of cholesterol.

Cholesterol injected into the circulation of rabbits is not accumulated in the blood to any large degree, but is rapidly deposited in various organs, while the elimination of it through the bile and urine is also greatly increased.

The focal infiltration of the kidney with cholesterol which occurs in hypercholesterolemia is accompanied by degenerative processes of the parenchymatous structures. The urine, as a rule, contains appreciable amounts of cholesterol.

A PHARMACOLOGIC AND CLINICAL STUDY OF PAPAVERIN *

DAVID I. MACHT, M.D.
BALTIMORE

Papaverin is one of the principal primary opium alkaloids in point of both quantity and pharmacologic interest. Its amount in opium varies from 0.1[1] to 0.2[2] per cent. The alkaloid was discovered by Merck in 1848. It crystallizes in white prisms, with a melting point of 147 C. The crystals are insoluble in water and alkalis, difficultly soluble in ether and benzol, but easily soluble in warm alcohol, chloroform and acetone. It is tasteless, is neutral in reaction with litmus and is polariscopically inactive. The alkaloid easily combines with acids, forming salts, and it is the sulphate and more especially the hydrochlorid that are chiefly used in physiologic work. These salts can be obtained on the market in a very pure chemical state, and are soluble in water and in normal saline. Like all the other opium alkaloids, papaverin is characterized by color reactions by which it can be identified and distinguished from the others. These color reactions have been recently well described by Warren.[3] The most characteristic are the deep rose color produced by Marquis' reagent (sulphuric acid plus formaldehyd) and the greenish-blue color produced by potassium ferricyanid and Marquis' reagent.[4]

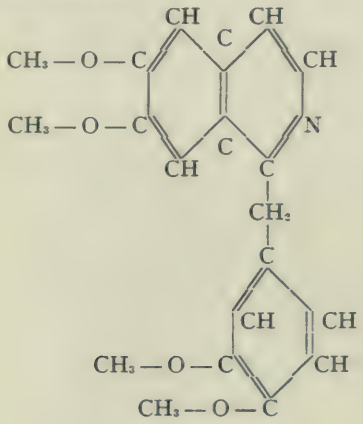
The empirical formula for papaverin is $C_{20}H_{21}NO_4$. Its chemical structure has been thoroughly worked out and is of great interest, not only in itself, but also as throwing light on the constitution of other opium alkaloids. A thorough analysis of its constitution finally enabled Pictet and Gams[5] to prepare it synthetically. Papaverin belongs to the so-called benzyl-isoquinolin group of opium alkaloids,[6]

* Submitted for publication, March 27, 1916.

* From the Departments of Pharmacology and Medicine, Johns Hopkins University.

1. Simon: Dissertation, Bern, 1903.
2. Henry: The Plant Alkaloids, 1913.
3. Warren: Am. Jour. Pharm., 1915, lxxxvii, 439.
4. Warren: Jour. Am. Chem. Soc., 1915, xxxvii, 2402.
5. Pictet and Gams: Beitr. z. Klin. d. Tuberk., xlii, 2943.
6. Winterstein and Trier: Die Alkaloide, 1910, p. 160.

the principal other constituent of which is narcotin. Its complete structural formula is as follows:



I. Pharmacology

The earlier pharmacologic experiences with papaverin are very few and limited. We need consider only the works of Claude Bernard and Baxt. Claude Bernard[7] denied to papaverin any narcotic properties, and classed it as a convulsant closely related to thebain. This view, which is a rather exceptional one, is as remarkable as the same author's attribution of powerful narcotic properties to the comparatively inert narcein. Sichting[8] from observations on himself and other human subjects concluded that papaverin is a mild narcotic. The most important and comprehensive of the earlier works on papaverin is that by Baxt.[9] Basing his conclusions on many animal experiments, Baxt claimed that papaverin is possessed of marked narcotic properties and is but slightly toxic for higher animals. The same author also called attention to its effect upon the frog's heart. Von Schroeder,[10] in his classic paper on the opium alkaloids, takes stand midway between Claude Barnard and Baxt, attributing to papaverin mild narcotic properties and also calling attention to the slowing of the frog's heart after injection of the drug. It is surprising to note that he failed to observe a fall in blood pressure, which is one of its striking characteristics.

Of the recent works on papaverin, by far the most important has been done by Pal of Vienna[11] and his school. To Pal belongs the

7. Cl. Bernard: Compt. rend. Acad. d. sc., lix, 464.
8. Sichting: Dissertation, Bonn, 1869.
9. Baxt: Arch. f. Anat. u. Physiol., 1869, p. 112.
10. Von Schroeder: Arch. f. Exper. Path. u. Pharmakol., 1883, xvii, 96.
11. Pal: Deutsch. med. Wchnschr., 1913, pp. 395, 2068, 2514; Wien med. Wchnschr., 1913, p. 1049; Zentralbl. f. Physiol., 1902, p. 68.

credit especially of calling attention to the action of papaverin on smooth muscle. It is strange to note, however, that although Pal has written much on the subject and tried the drug extensively in the clinic, he has published, with the exception of his work on the intestinal muscle, very few experimental data on the subject.

A more careful pharmacologic study of papaverin by the most modern methods was desirable, and it was undertaken by the present author in connection with a general study of the opium alkaloids individually and in combination with each other. The results were so interesting and so fraught with therapeutic possibilities, that it is deemed well to describe the pharmacology of papaverin with a few clinical experiences in a separate paper.

The most important pharmacologic properties of papaverin may be considered under four headings—its effect on the circulation, its effect on the respiration, its analgesic effect, and its action on smooth muscle structures.

A. ACTION ON CIRCULATION

Effect on the Heart.—If we excise a frog's heart and perfuse it with a weak solution of papaverin hydrochlorid (0.001 per cent. or less) in physiologic saline solution, a distinct slowing of the heart beat is noted, together with an increase in the toxicity of the heart muscle and more powerful contractions. If a stronger solution of papaverin is used (0.01 to 0.1 per cent.), the stimulating action is absent, and instead, a greater slowing of the beat and relaxation of the heart muscle are produced. Still stronger solutions lead to a further slowing and relaxation, and very often a heart-block effect is noted, the auricle beating oftener than the ventricle in the ratio of 2 to 1, 3 to 1 or even 4 to 1. Finally the heart comes to a standstill in diastole. This peculiar heart-block action is very similar to that produced by the closely allied alkaloid narcotin, as described by the author elsewhere.[12] Both Baxt and von Schroeder noted the toxic effect of large doses of papaverin on the frog's heart, but they failed to note the stimulating action of the drug when given in small doses (Fig. 1).

The stimulating action of papaverin on the heart is much better shown in mammalia and was studied by the author in the rabbit, cat and dog. This was done in part by perfusing excised hearts according to the methods of Martin or Langendorff, but was much more satisfactorily demonstrated by the study of the heart in situ with the chest opened, and the circulation intact. By the use of a cardiac plethysmograph or by direct myocardiographic tracings, it was found that small doses of papaverin produced a slight slowing of the heart beat and a marked increase in the tonicity of the heart muscles. The strength of the contractions and the volume output were also increased.

12. Macht: Am. Jour. Med. Sc., in press.

That this effect was not due to the action on the cardio-inhibitory center, was shown by cutting the vagi. That it was not due to the action of papaverin on the cranial autonomic nerve terminals in the heart, was shown by administering atropin, which paralyzed the vagus endings, but did not change the effect of papaverin. That this action on the heart was not due to any effect on the cardio-accelerator

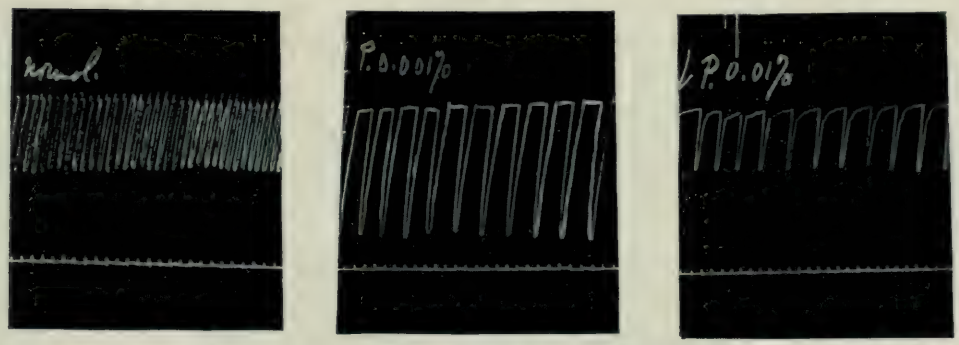


Fig. 1.—Effect of papaverin on a frog's heart. The down stroke represents the systole. Note slowing and increased contraction by a small dose (0.001 per cent.), and toxic effect of larger dose (0.01 per cent.).

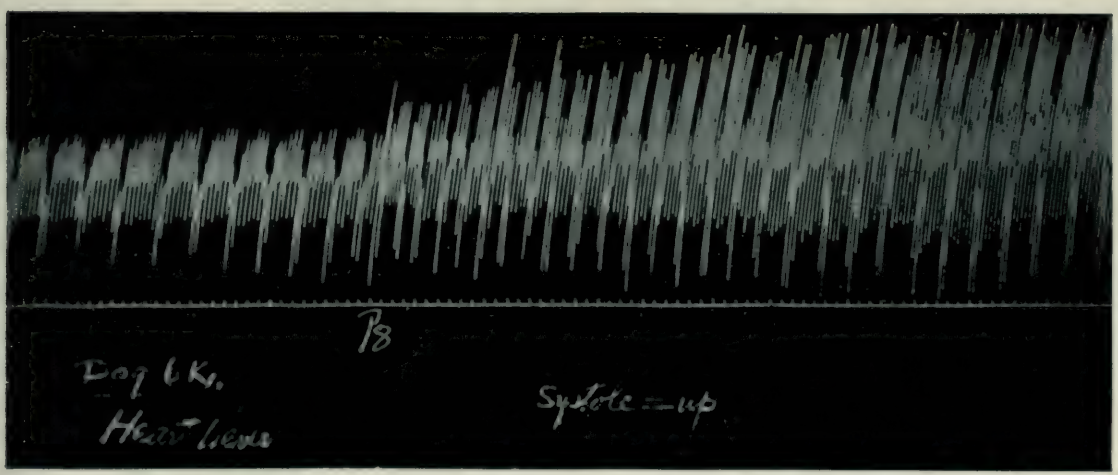


Fig. 2.—Action of papaverin on heart of dog; myocardial tracing.

mechanism, was shown by destroying the stellate ganglia. The stimulant effect was found to be due to a distinct action on the heart muscle itself or the ganglia in it. This was proved by experiments on decerebrated animals, on special preparations according to Sherrington,[13] and on excised frogs' and terrapins' hearts (Figs 2 and 3).

13. Sherrington: Jour. Physiol., 1909, xxxviii, 375.

Large doses of papaverin had relatively the same effect on the mammalian heart as on the frog's heart. They produced excessive slowing and paralysis of the heart, at which stage the toxic effect on the central nervous system also generally manifested itself in the form of convulsions.

Closely associated with the action on the heart is the effect of papaverin on the coronary arteries and the coronary circulation. This effect has been treated fully in a study of the effect of the principal opium alkaloids on the coronary circulation, published elsewhere,[14] and we will therefore merely sum up our findings here.

The action on the coronary circulation was studied in three ways: first by perfusion of excised hearts, especially by the recent method of Krafkoff;[15] second, by the study of excised rings of the coronary artery, and third, by ascertaining the effect on the coronary circulation

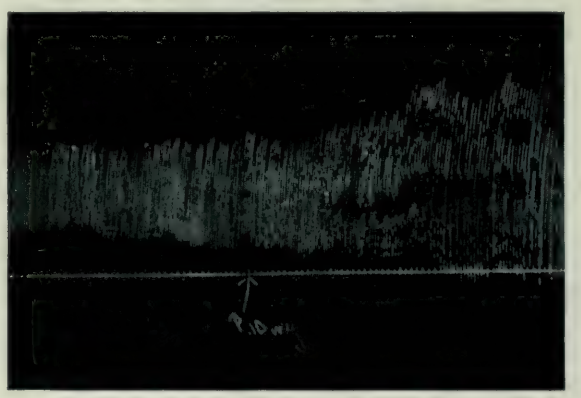


Fig. 3.—Action of papaverin on cat's heart. Heart is in a plethysmograph, the systole being represented by the down stroke.

in the living animal with chest opened and heart in situ, by recording the blood drop-flow from a wounded coronary artery, the blood having previously been hirudinized to prevent coagulation.[16]

By all the three methods it was found that papaverin is a powerful dilator of the coronary artery. Figure 4 shows this dilator effect on an arterial ring.

The following protocol illustrates the coronary dilatation as shown by Krakoff's method.

Experiment 10.—Perfusion of pig's heart by Krafkoff's method. The normal drop-flow was 25 drops per minute; after perfusion with 0.02 per cent. papaverin hydrochlorid solution the drop-flow was 46 drops per minute; five minutes later it became 56 drops per minute.

14. Macht: Jour. Am. Med. Assn., 1915, xliv, 1489.
15. Krafkoff: Arch. f. d. ges. Physiol. (Pflüger's), 1914, clvii, 501.
16. Bond: Jour. Exper. Med., 1910, xii, 575.

Figure 5 illustrates the increase in coronary circulation as indicated by the increased number of the blood drops flowing from an incised coronary in a hirudinized cat.

The coronary ring method could be practiced on the human as well as other coronary arteries, and it gave the same results.

Effect on the Blood Pressure.—The effect of a drug on blood pressure is a resultant of its effect on the heart, on the vasomotor appara-

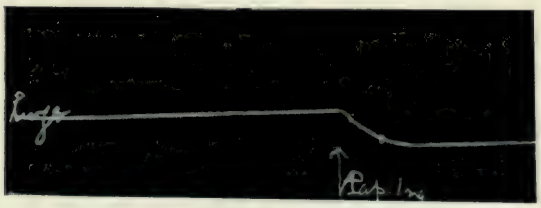


Fig. 4.—Action of papaverin on pig's coronary artery, three rings in chain; stretching weight 38 gm., lifting weight 18 gm. Note relaxation.

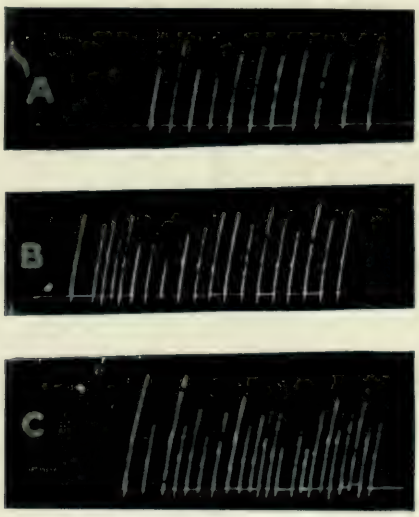


Fig. 5.—Experiment performed Dec. 22, 1914, on a cat of 2.5 kg., under ether anesthesia, and hirudin 20 c.c. Study of blood-flow from wounded coronary artery by Bond's method *A*, normal drop-flow, 11 per minute; *B*, drop-flow after injection of 8 mg. papaverin hydrochlorid, 18 per minute; *C*, three minutes later, 26 per minute.

tus and on the vessels themselves. These factors should be borne in mind in studying the effect of papaverin on the blood pressure. The most striking effect of papaverin in any blood pressure experiment on a rabbit, cat or dog—and the same is also true in man—is a fall in pressure. This fall in pressure was given after decerebrating the

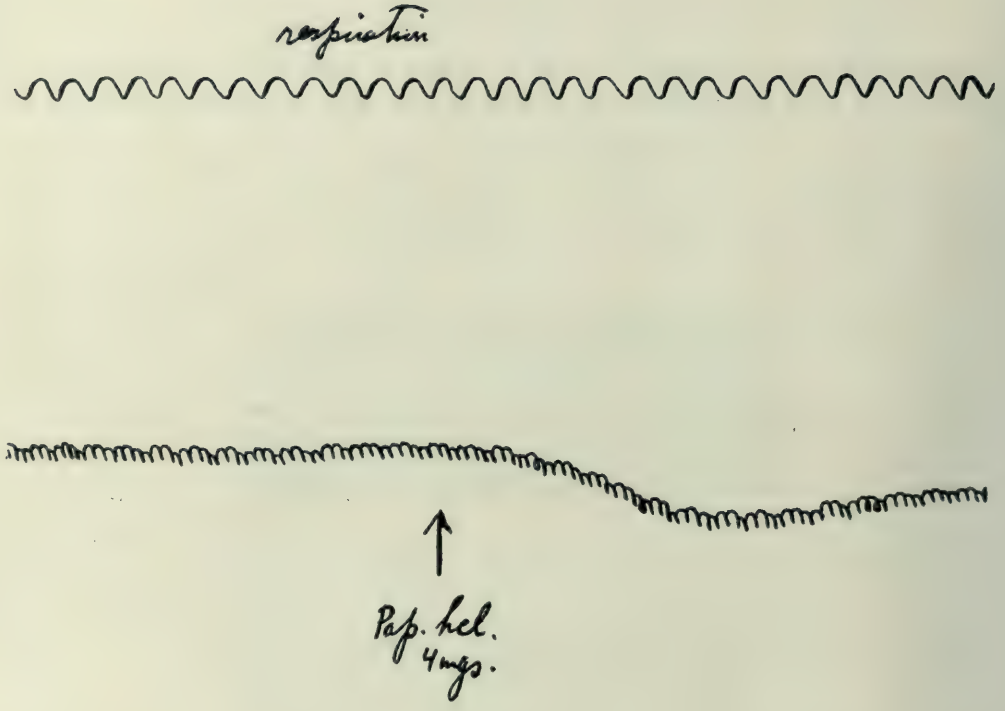


Fig. 6.—Experiment performed January, 1915, on a cat of 2.5 kg., ether anesthesia, showing effect of papaverin on blood pressure.

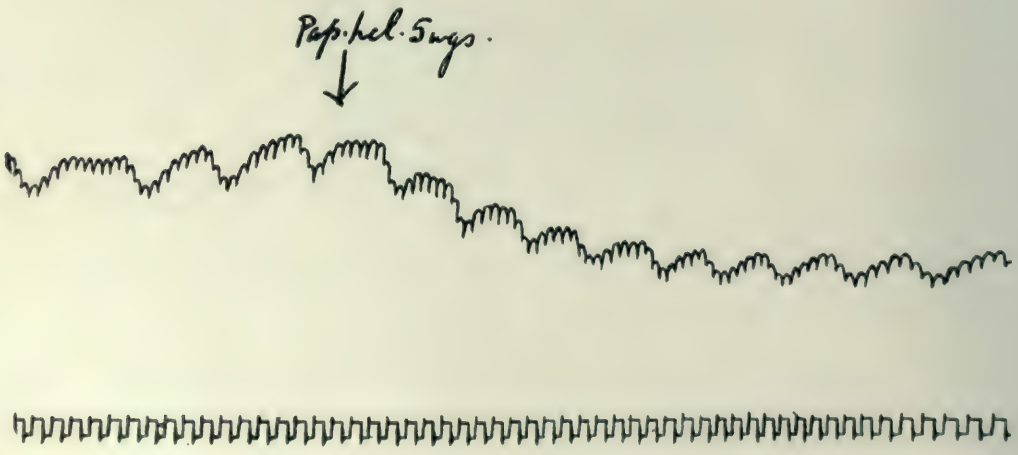


Fig. 7.—Experiment performed January, 1915, ether anesthesia, showing effect of papaverin on blood pressure with vagi cut.

animal through the orbit and also in Sherrington's spinal preparations. It follows, therefore, that the alkaloid produces the fall in pressure chiefly through its peripheral effect on the vessel walls themselves. The following curves and protocols will illustrate the above points.

Protocol 1: Experiment was performed Oct. 29, 1914, on a cat of 4 kg. Under ether anesthesia a spinal cord preparation, according to Sherrington, was made and curara administered. Normal blood pressure, 84 mm.; normal pulse, 68 per 30 seconds. Papaverin hydrochlorid, 15 mg., was injected into femoral vein. One minute after, blood pressure was 64 mm.; pulse, 68 per 30 seconds.; five minutes after blood pressure was 70 mm.; pulse, 70 per 30 seconds.

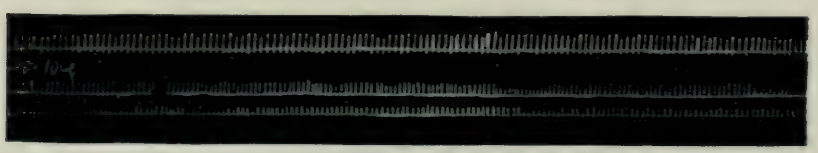


Fig. 8.—Perfusion of hind legs of *Rana pipiens*. Upper line gives number of drops on perfusing with normal saline; second line gives number of drops on perfusing with papaverin hydrochlorid, 0.01 per cent. solution in normal saline; lower line indicates time in seconds.

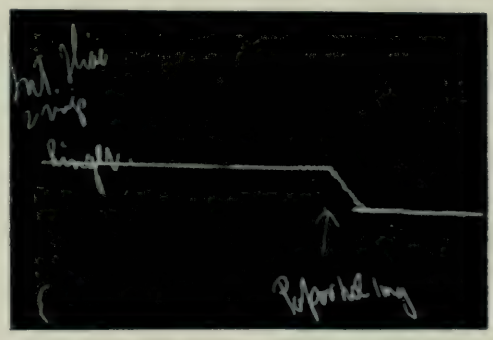


Fig 9.—Action of papaverin on internal iliac artery of pig. Two rings, stretching weight 30 gm., lifting weight 16 gm.

Protocol 2: Experiment was performed Jan. 8, 1915, on a cat of 2.5 kg. Under ether anesthesia decerebration was performed through the orbit. The normal blood pressure was 72 mm.; pulse, 65 per 30 seconds. Papaverin hydrochlorid, 10 mg., was injected into femoral vein. One minute after, blood pressure was 56 mm.; pulse, 66 per 30 seconds; five minutes after blood pressure was 66 mm.; pulse, 65 per 30 seconds.

Action on Blood Vessels.—The vasodilating action as noted in the blood pressure experiments could be shown by other methods.

The effect on the frogs' blood vessels was shown by perfusion of the hind legs by Trendelenburg's method. The action on the mammalian vessels was studied by means of arterial rings or strips,

described by the author elsewhere.[17] By this method it was interesting to note that different vessels differed in their reaction to papaverin. Whereas the coronary arteries, the carotids and subclavians, and internal and external iliacs were markedly relaxed by the drug, the pulmonary artery was but slightly dilated and the uterine arteries still less so. The effect on the mesenteric and splanchnic vessels was studied by means of the plethysmograph, and as might have been expected from the marked fall noted in blood pressure experiments, they were greatly dilated. This is well illustrated by the figures.

Summing up the circulatory effect of papaverin, we may therefore say that it causes a fall in blood pressure, which is due partly to its effect on the brain, but chiefly to its peripheral action; that it produces a marked vasodilatation, especially of the peripheral and splanchnic vessels; that it increases the coronary circulation, and that, in small

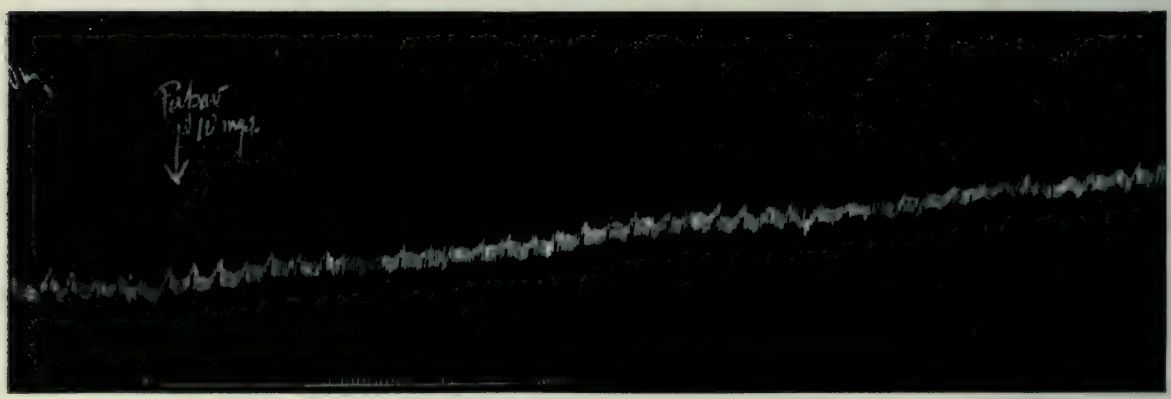


Fig. 10.—Effect of papaverin on intestinal vessels, as recorded by a plethysmograph. Curve upward indicates vasodilatation.

doses, it slows the heart, at the same time tending to increase the strength of its contractions.

B. ACTION ON THE RESPIRATION

The action of papaverin on the respiration has been touched upon by the author in another paper dealing with the action of opium alkaloids in general on the respiration.[18] There it was pointed out that the pharmacologic study of the respiration is a complex matter. It is not sufficient merely to determine the rate and volume output of respiration. Drugs may affect the respiratory function in several ways: by acting upon the respiratory center directly; by producing changes in metabolism; by altering the mechanical conditions of the

17. Macht: Jour. Pharmacol. and Exper. Therap., 1914, vi, 13.
18. Macht: Jour. Pharmacol. and Exper. Therap., 1915, vii, 339.

chest and abdomen; by acting on the bronchoconstrictors or bronchodilators; and indirectly by changes in the cerebral circulation, etc. Accordingly, in studying the action of papaverin on the respiration, observations were made on the rate of respiration, the total volume of air respired per minute or *total ventilation*, the true or *alveolar ventilation*, the effect on the respiratory center, and the effect on the bronchi. By the method described in the paper referred to, it was found that papaverin, while producing a slight narcotic effect upon the animal, exerts a distinctly stimulating effect on the respiration. While the rate of respiration is slightly decreased, the volume output and

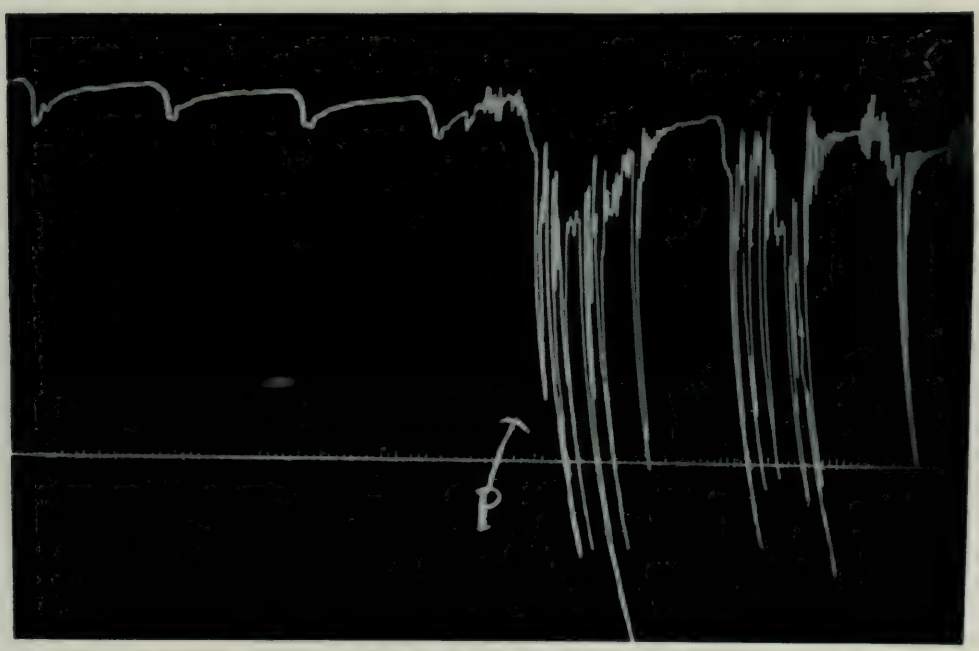


Fig. 11.—Experiment performed April 27, 1915. Perfusion of respiratory center by Hooker's method in a dog weighing 7.5 kg. At *P* 2 mg. of papaverin hydrochlorid were introduced. Note stimulation of center.

alveolar ventilation are markedly increased. The respiratory center is quite active as shown by its lively response to carbon dioxid inhalations, and the dead space is greatly enlarged, indicating a bronchodilatation. The bronchodilator effect was also proved directly by experiments with bronchial rings. The stimulating action of papaverin on the center was furthermore corroborated directly by perfusion of the medulla by Hooker's method.

The following protocols illustrate the above findings, and Figure 11 shows the result of a papaverin experiment on the medulla.

Experiment was performed Feb. 24, 1915, on a rabbit of 1,150 gm.; 11 a. m., rabbit tied down and allowed to get quiet.

Time	Breathing	Rate per min.	Vol. per min., c.c.	Vol. per resp., c.c.
11:30 a. m.	Air of room	68	450	6.6
	CO_2 5%	68	540	7.9
	CO_2 10%	68	640	9.4

11:50 a. m., injected subcutaneously papaverin hydrochlorid, 8 mg.

Time	Breathing	Rate per min.	Vol. per min., c.c.	Vol. per resp., c.c.
12:15 p. m.	Air of room	60	480	8.0
	CO_2 5%	64	520	8.1
	CO_2 10%	66	660	10.0
1:30 p. m.	Air of room	54	470	8.7
	CO_2 5%	60	520	8.7
	CO_2 10%	60	800	13.3
2:30 p. m.	CO_2 5%	58	500	8.6
	CO_2 10%	60	800	13.3

Experiment was performed March 11, 1915, on a rabbit of 910 gm. 2:00 p. m., animal tied down and allowed to quiet itself.

Time	Breathing	Rate per min.	Vol. per min., c.c.	Vol. per resp., c.c.
3:00 p. m.	Air of room	48	100	2.0
	CO_2 5%	46	200	4.3

Alveolar CO_2	5.7 per cent.
CO_2 of expired air	1.7 per cent.
Alveolar ventilation	29.8 per cent.
Calculated dead space	1.5 c.c.

3:35 p. m., injected subcutaneously papaverin hydrochlorid, 3 mg.

Time	Breathing	Rate per min.	Vol. per min., c.c.	Vol. per resp., c.c.
4:05 p. m.	Air of room	40	230	5.7
	CO_2 5%	40	400	10.0

Alveolar CO_2	6.8 per cent.
CO_2 of expired air	1.8 per cent.
Alveolar ventilation	60.8 c.c.
Calculated dead space	4.2 c.c.

C. ACTION ON SMOOTH MUSCLE STRUCTURES

Attention to this remarkable property of papaverin has been called by Pal, to whom we are indebted for arousing interest in the subject. Pal made a broad generalization to the effect that the alkaloid lowered the tonus and produced relaxation of all smooth muscle structures, without paralyzing them.

This generalization seems to have been based chiefly on Pal's clinical experiences, as his published experimental work is confined chiefly to studies of intestinal muscle. It is remarkable, however, to find that later observations by other investigators and the experimental work of the present author all seem to confirm fully the truth of Pal's

statement. The present author studied the action of papaverin on all kinds of smooth muscle organs, some of which had already been investigated and others of which were never examined, and found that in all cases the alkaloid produced a relaxation of smooth muscle.

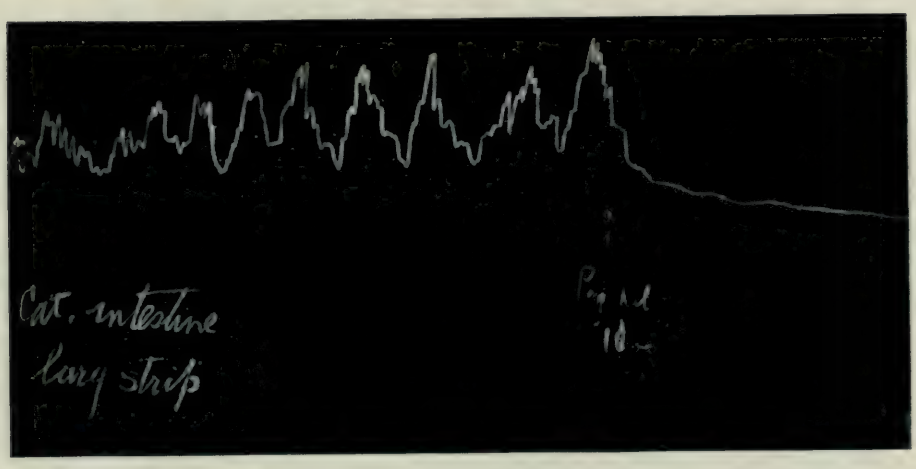


Fig. 12.—Action of papaverin on longitudinal muscle of cat's intestine.

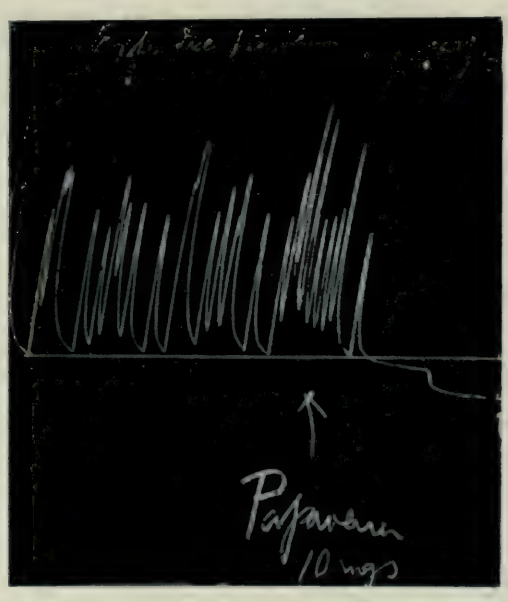


Fig. 13.—Action of papaverin on ureter of pig, three hours after excision. Upward stroke indicates the contraction.

The effect on blood vessels and bronchi has already been mentioned. The subjoined illustration (Fig. 12) shows the effect on intestinal muscle strips. The same result was found with strips of the

uterus and the bladder. In experiments on excised pyloric sphincters the present author could confirm the clinical experiences of Pal in pylorospasm. A relaxation of the sphincter was noted. Furthermore, one of the most interesting effects of papaverin to be mentioned in this place is its effect on the ureter. The present author found that this drug produces a marked relaxation of that organ and this effect is of practical interest as will be shown later (Fig. 13).

D. ANALGESIC PROPERTIES

Attention to the narcotic and analgesic properties of papaverin has been especially directed by Baxt. That author claimed for the drug these properties in a high degree. Fronmüller[19] also emphasized the analgesic effect of papaverin. On the other hand Claude Bernard, Sichting, Eulenburg[20] and von Schroeder, considered the alkaloid in this respect as of very little importance. The explanation for the wide differences of opinion on the subject was chiefly due to the lack of an adequate method of comparing the effect of opium alkaloids on pain quantitatively. In a paper on the subject published elsewhere, the present author elaborated a simple method for a quantitative study of pain stimuli on the surface of the body, and the effect of papaverin was investigated in that connection.[21]

It was found that papaverin possesses analgesic properties in a higher degree than codein, the effect of 40 mg. being not much inferior to that produced by 10 mg. of morphin. The onset of the analgesia, however, was much slower and its duration shorter. The general narcotic effect and depression of the higher centers was, on the other hand, much less than that from morphin.

Observations were made on six normal individuals, and the results, barring slight individual variations, agreed in all cases. The following protocols will serve as illustrations. It will be noted that injections of papaverin are slightly painful at the site of injection, but this discomfort soon passes away.

E. TOXICITY

Before discussing the therapeutic applicability of papaverin, it is essential to consider its toxicity. Papaverin is not a very poisonous drug and comparatively large doses of it can be given without dangerous results. Indeed the lethal dose for higher animals is so large that for economic reasons it was not deemed profitable to push the drug till death was produced in too many experiments. It was suffi-

19. Fronmüller: Klinische Studien über narkotische Arzneimittel, Erlangen, 1869.

20. Eulenburg: Die Hypodermotische Injection der Arzneimittel, Berlin, 1867.

21. Macht, Herman, and Levy: Jour. Pharmacol. and Exper. Therap., 1916, viii, 1.

TABLE 1.—Experiment Performed July 10, 1915, 2:20 p. m.

Subject D. I. M. Injection of papaverin sulphate, 40 mg.

	Hand			Tongue			Lip			Nose		
	Position of Secondary, Cm.	Kronecker Units	C. G. S. Units	Position of Secondary, Cm.	Kronecker Units	C. G. S. Units	Position of Secondary, Cm.	Kronecker Units	C. G. S. Units	Position of Secondary, Cm.	necker Units	C. G. S. Units
Normal	11.8	155	2,829	14.4	55	1,173	16.8	26	639	17.7	20	518
30 min. after injection	10.2	270	5,313	12.9	100	1,897	14.0	65	1,346	14.6	51	1,139
1 hr. after injection	9.7	320	6,210	12.4	125	2,277	13.3	87	1,656	12.2	137	2,484

Remarks. Pulse: before injection, 72; after injection, 66; blood pressure: before, systolic, 105, diastolic, 80; after, systolic, 98, diastolic, 78. Fullness in head after injection; slight pain at place of injection; very slight feeling of heaviness and dulness in ears; no constipation.

TABLE 2.—Experiment Performed July 8, 1915, 2:20 p. m.

Subject C. S. L. Injection of papaverin hydrochlorid, 40 gm.

	Hand			Tongue			Lip			Nose		
	Position of Secondary, Cm.	Kronecker Units	C. G. S. Units	Position of Secondary, Cm.	Kronecker Units	C. G. S. Units	Position of Secondary, Cm.	Kronecker Units	C. G. S. Units	Position of Secondary, Cm.	necker Units	C. G. S. Units
Normal	10.0	285	5,520	15.9	33	795	14.3	57	1,244	16.2	29	742
15 min. after injection	8.5	425	8,694	14.9	48	1,036	12.8	105	1,966	15.2	42	966
30 min. after injection	8.6	420	8,349	14.2	60	1,278	12.0	145	2,622	15.5	38	915

Remarks.—Pulse: before injection, 84; after injection, 84. Blood pressure, before injection, systolic, 102, diastolic, 70; after injection, systolic 98, diastolic, 64. No untoward symptoms.

TABLE 3.—Experiment Performed July 15, 1915, 10:40 A. M.

Subject N. B. H. Injection of papaverin hydrochlorid, 35 mg.

	Hand			Tongue			Lip			Nose		
	Position of Secondary, Cm.	Kronecker Units	C. G. S. Units	Position of Secondary, Cm.	Kronecker Units	C. G. S. Units	Position of Secondary, Cm.	Kronecker Units	C. G. S. Units	Position of Secondary, Cm.	necker Units	C. G. S. Units
Normal	13.2	89	1,725	19.0	15	408	16.0	31	778	19.7	13	311
20 min. after injection	12.5	120	2,208	18.2	17	466	14.8	48	1,070	18.3	17	449
40 min. after injection	12.3	130	2,346	18.1	17	474	14.6	51	1,139	18.0	18	483

Remarks.—Pulse: before injection, 70; after injection, 64. Systolic pressure: before injection, 108, after injection, 103. No discomfort following injection, except slight soreness of arm; no constipation; no nausea.

cient for all practical purposes to ascertain the quantity of the drug which produced toxic symptoms.

In the frog it was found that the minimal lethal dose was about 1 mg. per gram weight of frog. These results agreed well with those of von Schroeder.

In the guinea-pig 100 mg. administered subcutaneously stimulated respiration; 200 mg. produced violent convulsions, and death in about ten minutes. A similar experience with guinea-pigs is reported by Bradbury.[22]

White mice required about 0.5 mg. per gram weight to produce convulsions and death in half an hour.

In rats, according to Bradbury, 300 mg. produced weakness of the muscles, but no death.

In the case of rabbits different experimenters show considerable variations in their figures. According to Bradbury it required 480 mg. to produce death. Kunkel[23] claims that doses up to 1 gm. produce muscular weakness, and larger doses produce convulsions and death, but he does not state whether the drug was given by stomach or by injection. Lewin[24] gives 2 gm. as the lethal dose by mouth. In the present author's experiments the drug was not pushed to a lethal outcome; but it was found that doses of 25 mg. per kilo, subcutaneously, excited the animal, but did not cause death, while repeated doses of 10 mg. each, every five to ten minutes, intravenously, caused convulsions, after five or six doses.

In cats the present author found that 55 mg. per kilogram, subcutaneously, produced no untoward symptoms. Repeated intravenous injections of 10 mg. doses in cats of 2.5 to 3 kg. produced convulsions after six doses.

In dogs Baxt noted marked anesthesia after 100 mg. In the present author's experience subcutaneous injections of 50 mg. per kilogram produced distinct narcosis with uneventful recovery. Intravenous injections in doses of 10 mg. every five minutes produced convulsions in a dog of 6 kg. after about 100 mg. were injected.

In reference to the safe dosage for man, we have collected considerable data. Schroff and Hoffman[25] state that doses of 450 mg. produce no effect. Fronmüller injected subcutaneously 240 mg. without harmful results. Leidesdorff[26] injected insane patients with doses of over 400 mg. without danger. Blyth[27] puts 1 gm. as the dosage

22. Bradbury: Lancet, London, July, 1899.
23. Kunkel: Toxikologie, 1901, ii, 820.
24. Lewin: Toxikologie, Berlin, 1897, p. 260.
25. Schroff and Hoffman: Wien. med. Wchnschr., 1868, pp. 935 and 952.
26. Leidesdorff: Ztschr. d. Wien. Aerzte, 1868, xiii, 115.
27. Blyth: Poisons, London, 1906, p. 322.

limit, and Pal quotes Bouchut also as giving quantities up to 1 gm. subcutaneously. These doses, however, are certainly not to be considered safe at present, and Lewin cites a case with some weakness produced by 180 mg. Pal recommends 40 to 80 mg. subcutaneously as perfectly safe doses, and states that higher doses also produce no harmful results. The author's experience with the drug on himself, colleagues and patients certainly agrees with Pal's, so that doses of from 40 mg. to 80 mg. subcutaneously, in adults, may certainly be administered without trepidation.

The present author injected papaverin intravenously on three occasions without any untoward symptoms. It was found that 40 mg. well diluted with 200 c.c. of saline and injected slowly could be administered safely.

No cumulative action from papaverin has been noted by the author. Repeated intravenous injections of from 10 to 20 mg. of the hydrochlorid daily over periods of from two to three weeks showed no such effect in rabbits or dogs. Papaverin is for the most part unchanged in the body, and is excreted chiefly through the urine, bile, and partly through the small intestine. *

II. Clinical Experiences

The clinical application of papaverin should of course follow its physiological behavior. This has been done, in a measure, by Pal and his school. Thus its peculiar effect on the circulation, promoting the coronary circulation, lowering the pressure and stimulating the heart, will suggest its use in angina pectoris and in cases with hypertension. Pal actually employed it in aborting uremic crises.[29]

Its stimulating effect on the respiratory center would suggest its use in cases where depression of that center is undesirable.

Its analgesic action would suggest its use as a substitute for morphin, especially where codein is not effective.

Lastly, its peculiar action on smooth muscle would indicate its use in all cases with visceral spasm.

In the present communication, the author is reporting his rather limited experience with the drug, not so much as a positive proof of the therapeutic value of papaverin, as in order to stimulate further observation. The following cases were selected more or less at random, and papaverin was administered in some cases to relieve pain and in others for the purpose of exhibiting its other properties. The results seem to be encouraging.

On examining the histories, one will note that in regard to its pain-relieving quality papaverin, though inferior to morphin, is cer-

* Dragendorff: Ermittelung von Giften, 1895, p. 225.

28. Bouchut: Cited by Pal in Med. Klin., Nov. 2, 1913, No. 44.

29. Pal: Med. Klin., Nov. 2, 1913, No. 44.

tainly equally as efficient as, and even more efficient than, codein. It will also be noted that it was more or less efficient in the cardiac cases (Cases 14, 15, 22, 27, 28, 30). In the respiratory conditions the effect was not so marked, but attention is called to Case 5, in which it was efficacious in relieving the troublesome cough of an advanced consumptive, who was habituated to heroin; and its really striking relief of the cough in the case of aneurysm, No. 7, which was not relieved by any other drug.

The employment of papaverin in bronchial asthma was recommended by Pal. In Case 10, the effect of papaverin on bronchial asthma in a boy of 15 years was immediate. Case 11, however, another case diagnosed as "asthma," was not relieved; but neither was that patient relieved by epinephrin or atropin.

Cases 13 and 25 illustrate the effect of papaverin in relaxing the spasm of biliary ducts, and other successful examples of the antispasmodic properties of the drug are found in Cases 12, 17, 18, and 21.

The peculiar property of papaverin in relaxing the tonus and contractions of smooth muscle organs led Pal to recommend it in cases of pylorospasm. Its value in such cases was demonstrated by Holzknecht and Sgalitzer[30] through their Roentgen-ray studies, and it has recently been further recommended by Delprat.[31] All these authors administered papaverin by hypodermic injection. Inasmuch as a very striking effect is produced by the drug on smooth muscle in vitro, and that by very small doses, as shown by Popper,[32] it occurred to the present author that papaverin might in such cases be advantageously given by mouth, and in fact two or three cases of pylorospasm treated in this way in the Harriet Lane Home for Invalid Children (Professor Howland) gave favorable results.

Another application of the tonus-relaxing quality of papaverin suggested by the present author was its introduction directly into the ureter through a cystoscope, in cases of ureteral calculus and colic. Observations along this line are being carried on at the James Buchanan Brady Urological Institute (Professor Young). It may be here stated that two cases of ureteral stone were successfully treated by Dr. T. I. Gerathy in this way.[33]

SYNOPSIS OF CLINICAL CASES

CASE 1.—S. M., dispensary case, F. 39372. Acute gastric indigestion. Forty mg. hypodermically. Slight relief.

CASE 2.—M. G., dispensary case, E. 91401. Severe cramps in one leg. Tablets 40 mg. each, three times a day by mouth. Distinct relief.

30. Holzknecht and Sgalitzer: Munch. med. Wchnschr., 1913, No. 3.
31. Delprat: Nederl. Tijdschr. v. Geneesk., 1915, ii, 1311.
32. Popper: Arch. f. d. ges. Physiol. (Pflüger's), 1913, cliii.
33. Gerathy and Macht: Bull. Johns Hopkins Hosp., 1916, xxvii, 119.

CASE 3.—A. C., dispensary case, F. 33848. Very persistent cough; tuberculosis. Tablets 40 mg. each, three times a day. Slight relief.

CASE 4.—J. Y., dispensary case, F. 36190. Chronic bronchitis and emphysema; persistent cough. Tablets 40 mg. each, three times a day. No relief.

CASE 5.—P. R., outside case, white woman, 23 years of age. Advanced tuberculosis. Codein has no effect. Dionin and heroin have very little effect because of habitual use for cough. Tablets of papaverin, 40 mg. each, patient says relieved her a little more than heroin.

CASE 6.—H. M., dispensary case, E. 58406. Tuberculous laryngitis and phthisis. Marked relief of cough and pain from tablets of papaverin hydrochlorid, 40 mg.

CASE 7.—J. B., dispensary case, F. 38599. Aortic aneurysm; troublesome cough. Patient tried morphin, heroin, codein, narcophin. Finds that papaverin tablets, 40 mg. each, relieve better than any other drug. Same experience repeatedly.

CASE 8.—W. D., dispensary case, E. 59866. White man, 36 years of age. Lumbago. Relieved by injecting 40 mg. of papaverin sulphate. Pulse before injection 72, after injection 68 per minute.

CASE 9.—S. G., outside case. White man, 35 years of age. Acute gastric indigestion. Injection of 40 mg. papaverin sulphate with slight relief. Pulse before injection 88, after injection 72 per minute.

CASE 10.—B. H., outside case. White boy, 15 years of age. Bronchial asthma. Injection of 30 mg. papaverin sulphate. Immediate relief.

CASE 11.—Dr. L. Karlinski's case. White woman. "Asthma." Papaverin injection does not relieve. Epinephrin injection gives no relief, but aggravates condition. Only drug giving any relief is morphin.

CASE 12.—R. A., outside case. White woman, 26 years of age. Uterine colic. Relieved by injection of 40 mg. papaverin sulphate.

CASE 13.—R. S., dispensary case, F. 30928. White woman, 32 years of age. Gallstone colic. Two attacks, at different times, promptly relieved by injections of 40 mg. papaverin sulphate. A third time patient had attack at home, and called a physician, who gave her an injection of morphin. Patient was made "sleepy," but relief was not as prompt as from papaverin.

CASE 14.—M. E., outside case. White man, 46 years of age. Myocardial insufficiency. Dyspnea and precordial pain relieved temporarily by injection of 40 mg. papaverin sulphate.

CASE 15.—M. B., outside case. White woman, 64 years of age. Anginal pains and dyspnea from myocardial and arteriosclerotic changes. Relieved temporarily by injection of 40 mg. papaverin sulphate. Pulse distinctly fuller and pressure lower after injection.

CASE 16.—M. H., outside case. White woman, 26 years of age. Acute neuritis of right hand and forearm. No relief from papaverin injection of 40 mg.

CASE 17.—Dr. F. P., 56 years of age. Renal colic; very severe, requiring chloroform inhalations and morphin. Slight relief experienced for an hour or two after injection of 40 mg. papaverin sulphate.

CASE 18.—R. G., dispensary case, F. 23824. White man, 32 years of age. Lead colic. Distinct relief from injection of 40 mg. papaverin sulphate. Pulse before injection 80, after injection 72 per minute.

CASE 19.—N. J., outside case. Man, black, 40 years of age. Acute enteritis. Pain was relieved by injecting 40 mg. of papaverin sulphate. He came next day asking for another injection.

CASE 20.—M. K., outside case. White woman, 38 years of age. Severe nervous headache, relieved by injecting 40 mg. of papaverin sulphate.

CASE 21.—M. K., outside case. White woman, 30 years of age. Acute vesical spasm. Pain relieved very quickly by injection of 40 mg. of papaverin sulphate.

CASE 22.—M. B., outside case. White man, 56 years of age. Anginoid attacks. Relieved by 40 mg. of papaverin hydrochlorid in solution by mouth every four hours.

CASE 23.—M. S., outside case. White man, 60 years of age. Cardiac dyspnea, very bad. Very little relief from injection of 40 mg papaverin.

CASE 24.—J. W., Ward F. (care of Dr. F. A. Evans). Hysteria. Injection of 40 mg. papaverin sulphate for nervousness and insomnia; not efficacious.

CASE 25.—S. W., Ward O (care of Dr. F. A. Evans). Hyperacidity and gallstones (?). Injection of 40 mg. papaverin sulphate for a paroxysm of pain brought about complete relief in fifteen minutes. Before injection respiration 24, pulse 84, blood pressure, systolic 165, diastolic 95; after injection respiration 26, pulse 70, blood pressure, systolic 140, diastolic 90.

CASE 26.—J. W., Ward F (care of Dr. F. A. Evans). Psychasthenia malignum; hysteria. Injection of 40 mg. papaverin sulphate for nervousness and insomnia proved efficacious; slept all night. Before injection respiration 24, pulse 88; half hour after injection respiration 24, pulse 84.

CASE 27.—A. B., Ward F (care of Dr. F. A. Evans). Syphilis of aorta; aortic insufficiency; myocardial insufficiency. Injection of 40 mg. papaverin sulphate for dyspnea and restlessness. Quieted a little after administration; slept brokenly several hours. Before injection respiration 30, pulse 80; half hour after injection respiration 30, pulse 80.

CASE 28.—E. M., Ward F (care of Dr. F. A. Evans). Hypertension; myocardial failure. Injection of 40 mg. papaverin sulphate for dyspnea and restlessness. Quite efficacious; patient almost asleep in ten minutes. Before injection respiration 32, pulse 94, blood pressure, systolic 185, diastolic 100; after injection respiration 26, pulse 93, blood pressure, systolic 185, diastolic 95.

CASE 29.—T. H., Ward F (care of Dr. F. A. Evans). Lobar pneumonia; pericarditis. Injection of 40 mg. papaverin sulphate not efficacious in relieving pleural pain. Neither is relief given by injection of ⅙ grain morphin.

CASE 30.—J. D., Ward F (care of Dr. F. A. Evans). Aortic insufficiency; bronchopneumonia. Injected 40 mg. papaverin sulphate for relief of cough, dyspnea and restlessness. Quite efficacious, asleep in thirty-five minutes and slept five hours. Before injection respiration 28, pulse 100; after injection respiration 24, pulse 98.

CASE 31.—G. G., Ward F (care of Dr. F. A. Evans). Pneumonia; pneumothorax. Injected 40 mg. papaverin sulphate to induce quiet sleep. Not asleep in half hour, but quiet and drowsy. Before injection respiration 30, pulse 128; after injection respiration 30, pulse 112.

CASE 32.—R. A., Ward O (care of Dr. F. A. Evans). Bronchopneumonia. Injection of papaverin sulphate for dyspnea and restlessness. Not efficacious; some infiltration at site of injection next day.

SUMMARY

From the above data, it will be seen that the alkaloid papaverin exhibits certain very interesting pharmacologic properties. Chief among these are its effect on the heart and blood pressure, its action on the coronary circulation, its stimulating effect on the respiration, its relaxing and tonus-lowering influence on the smooth muscle structures, and its considerable analgesic power.

These, together with its comparatively low toxicity, suggested its employment for therapeutic purposes. The clinical experiences described speak in its favor, and it is hoped that further observations may be made to determine its exact therapeutic value in medicine.

A CLINICAL HEMOGLOBINOMETER*

HERBERT HAESSLER
AND
HARRY S. NEWCOMER, M.D.
PHILADELPHIA

We have devised a colorimeter for the clinical estimation of hemoglobin which possesses several advantages over instruments now in use. Those methods for the estimation of color density, which depend upon the comparison of a sample with an interrupted series of standards, have always been the most satisfactory. The eye is able to place a sample with more certainty between two members of a variable series than it is to compare a sample with a uniformly graded scale. The latter only becomes accurate when the error is absorbed into a great number of readings, and as yet there had been no instrument devised superior to the Fleischl-Miescher for such a procedure. For a single operation, comparison with a series offers much more certainty as to the correctness of the choice.

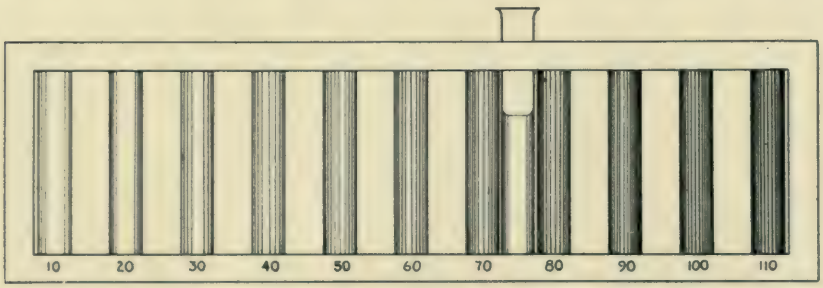
We have adopted the principle of the Sahli hemoglobinometer, modifying it to satisfy the above concepts. The Sahli instrument has the advantage that it offers a comparison color of the same material as the sample, and a color to whose shade variations the eye is particularly sensitive. It has the disadvantage of uncertainty of comparison, due to the fact that one cannot reconsider a discarded choice. Therefore, instead of the single standard tube, we use eleven comparison tubes, whose densities correspond to readings varying by 10 from 10 per cent. to 110 per cent. hemoglobin. The standard fluids are made up according to Sahli's specifications. The tube marked 100 per cent. contains in 10,100 c.c. the equivalent in hematin hydrochlorid of 17.2 gm. of hemoglobin. Sahli bases his percentage readings on blood containing 17.2 gm. hemoglobin per 100 c.c. Such a blood, diluted 1 to 100, would then correspond exactly with the mixture in our 100 per cent. tube.

Our procedure for the preparation of the standards is as follows: Ten c.c. of human blood are drawn from a vein into a certified pipet and immediately emptied into and rinsed in 100 c.c. of 10th normal hydrochloric acid. At the same time, from the same vein, 2 c.c. of blood are drawn into a 2 c.c. pipette and emptied into and rinsed in 400 c.c. of 1 per cent. sodium carbonate solution. This latter solution

* Submitted for publication, April 1, 1916.
* From the Ayer Clinical Laboratory of the Pennsylvania Hospital

is then calibrated on a Fleischl-Miescher hemoglobinometer and the hemoglobin of the blood determined in grams per 100 c.c. The hydrochloric acid mixture is then made up with tenth-normal hydrochloric acid in dilutions corresponding to 17.2 gm. hemoglobin per 10,100 c.c. of fluid for the 100 per cent. tube and fractions of that for the other tubes.

The hematin hydrochlorid is insoluble and forms a fine suspension. This settles easily. For that reason beads are enclosed in the tubes so that the fluid can easily be made homogeneous by a little shaking. It is impossible to seal the tubes off short above the fluid. A very satisfactory and simple method is to partially close them and then seal with a plug of paraffin dropped in from a pipet. Experiment showed that the eye can most readily compare colors in the form of vertical rectangles, and the size and shape eventually used seems to be the most favorable one. The tubes are made from glass tubing which to the eye



Hemoglobinometer with comparison tube containing a test specimen in the rack but not at the correct reading; scale six-tenths natural size.

has a uniform thickness and whose outside diameter (about 7 mm.) does not vary by more than one-tenth mm. Such tubing is easy to pick out of ordinary stock.

The tubes are conveniently arranged in a rack, so that the comparison tube can be slipped in between any two of them. The frame measures 5½ by 18 cm. It is of red vulcanized fiber, which is cheaper and more durable than gutta-percha, and the color of which does not seem to be objectionable. Septa between the tubes and opal glass behind them have been tried and discarded. The simpler construction facilitates the reading. Reflected light obtained by placing the instrument on a sheet of paper, as is done in ordinary titration, is best suited for the readings.

On placing the comparison tube in the rack, a malposition immediately strikes the eye as producing a sharp discontinuity, as is shown by the accompanying illustration of the instrument. On moving the tube one way or the other in the rack the point at which the shading

becomes harmonious is readily found and the amount of deviation from one of the multiples of ten estimated.

The dilution of the patient's blood can well be done with an ordinary red blood pipet, using tenth-normal hydrochloric acid as a diluting fluid. A dilution of 1 to 100 is made. The red blood pipet will deliver enough fluid to fill the comparison chamber, and it offers a convenient and accurate instrument for the purpose with the additional advantage that it is usually already available or readily obtainable.

The readings can be made in any light and with certainty to a multiple of 5 or in other words to within 2½ of the correct percentage.

The frame is also very convenient when made up to use as a phenolsulphonephthalein colorimeter. For this purpose, however, it will never be as satisfactory as those instruments in which the standard solution can be made up each time fresh with a specimen of the urine as a diluent.

THE USE OF THE "KARELL CURE" IN THE TREATMENT OF CARDIAC, RENAL AND HEPATIC DROPSIES *

EDWARD HARRIS GOODMAN, M.D.
PHILADELPHIA

The various measures recommended for the successful treatment of failing cardiac, renal and hepatic functions, with their concurrent edema of more or less severity, are legion, and one would be unwise to undertake the treatment of such conditions without a full appreciation of the value of each. Drugs, physical therapeutics and diet form the triad upon which reliance is usually placed, and generally speaking, in the lay as well as in the professional mind the greatest of these is drugs. There are many dropsical cases in the treatment of which one must use all three; there are many in which physical measures may be safely dispensed with, and there are many cases of severe renal and cardiac breakdown in which drugs as well as physical measures may be disregarded; but there are none in which diet has not earned a well-deserved and fixed place.

It may be stated without fear of serious criticism, that the majority of cardiac dropsies and a large proportion of dropsies of renal origin will improve with the combination of rest in bed and an appropriate diet. The diet which has served me best and which I have employed successfully for some time is that known as the Karell diet, or the Karell cure. Although half a century has elapsed since Karell published his paper (1866), this particular form of diet bearing his name seems to be but little known and but rarely used. In Germany it is slowly finding its place, but as recently as 1908 Jacobs[1] wrote that he could find no mention of it in the textbooks, and but little practical knowledge of its existence among physicians. In America it is known, but not intimately, and it has not secured for it the acclaim which would be its portion were it employed more frequently.

During my association with Dr. John H. Musser in the Presbyterian and University hospitals, and with Dr. James E. Talley in the former institution, I have been given the opportunity to make free use of this method of treatment during the past few years, and have employed this diet in many cases, between a hundred and a hundred and fifty approximately. This experience, which has been productive of

* Submitted for publication March 23, 1916.
* Read before the College of Physicians, Philadelphia, April 5, 1916.

1. Jacobs: München. med. Wchnschr., 1908, lv, 839.

improvement in the majority of these patients, is the raison d'être of this paper.

The technic of the Karell cure is simple and easily carried out as far as the physician is concerned. The patient receives daily at 8 a. m., 12 m., 4 p. m., and 8 p. m. 200 c.c. of raw or boiled milk, warm or cold, according to taste. No other food or liquid should be given. This strict diet sometimes, nay, many times, meets with violent opposition from the patient, and great complaint is made because of thirst. Thirst is particularly tormenting during the first three or four days of the "cure," and often it becomes necessary to allow the patient to rinse out his mouth with water, instructing him to swallow none, however. Hunger is not so common a complaint, but when urgent, a small piece of dry toast or zwieback may be given with each portion of milk. During the first few days the patient requires continual encouragement to persist with the treatment, but the moral effect of the rapid loss of weight, as shown by daily weighings, together with the very evident decrease of the edema, prove sufficient argument to him, and no further complaint is heard. Just how long this very strict diet is to be continued depends on the rapidity with which edema diminishes and on the patient's plea for more food. Usually the diet may be increased at the end of a week's time by giving a soft-boiled egg, without salt or pepper, at 10 a. m., and a piece of zwieback at 6 p. m. The next day an egg may be given at 10 a. m. and at 2 p. m., with a piece of white bread, and from now on food is gradually increased until a full diet is being taken. During this time the daily quantum of liquid should not exceed 800 c.c., and this fluid should be in the form of milk, until the patient receives a full diet, when the milk may be discontinued and cocoa or tea substituted, the amount of liquid remaining the same, however. No more than 800 c.c. of fluid should be taken for from two to four weeks after the disappearance of edema.

The "full diet" spoken of above is a misnomer, for the diet should be salt poor, and the following foods comprise this dietary: meat, fresh-water fish, cream soups, fresh eggs cooked in any form or raw, rice, corn, hominy, Indian corn, endives, peas, string beans, French beans, artichokes, onions, leeks, carrots, salads except lettuce, cauliflower, potatoes, cereals of all kinds, butter unsalted, bread without salt, sweetmeats, sugar, chocolates, cocoa, tea, coffee, fruits, milk, cream cheese and Swiss cheese, puddings, junket, ice-cream.

During the "cure," which it seems needless to say must be carried out with the patient in bed, the bowels must be kept open, and for this purpose laxatives in pill form are preferable to salines, merely because they require no water for their administration. In a typical case, that is, in those individuals who begin to lose weight through the loss of edema, and who show increased diuresis, no other medication is

required, but where improvement is not seen at the end of three days, or when symptoms are urgent, such as dyspnea, oppression, restlessness, unduly frequent and weak pulse, or active uremic signs, the drugs and other measures usually indicated in such conditions should be used. This question will be further discussed later on.

The article by Karell[2] in which he described his milk cure was published in 1866 and apparently was entirely forgotten, and would no doubt have remained in obscurity, had not Jacob[1] reported the results obtained with it in Lenhartz clinic, where it had been used for about fifteen years. Just how many of the few writers on the subject have read Karell's original paper it is impossible to say, but Jacob has given the year of publication as 1868 instead of 1866, and his error has found its way into practically every article since 1908, so that the inference that few have read the original is perhaps justified. Possessed as it is of great practical interest and of historical interest as well, written in a peculiarly intimate manner and naïve in spirit, Karell's paper should be read at first hand, but I can not forbear quoting at length from this very interesting article. He writes:

> It is always with a rich profusion of remedies and with the greatest confidence in their efficacy that the medical youth enters upon the practical exercise of his profession. However, experience does not long delay in demonstrating the inanity of that pretended richness; the circle of medicines prescribed narrows year by year and the physician whose age has ripened talent finally finds himself obliged to confess that the surface of his finger nail would be large enough upon which to inscribe the names of the medicines used in practice.
>
> If I confess to something of the same nature, if at the end of thirty-four years of practice a sort of skepticism takes possession of my spirit, relative to the curative virtue of many medicaments, I have, on the other hand, gained faith in the efficacy of certain means whose object is to change and to modify nutrition.
>
> If I call attention today to the methodical cure by means of milk, I do it in the firm conviction that the number of cures brought about by this treatment is due, in large part, to the judicious use and to the strict observance of the method. It is only thus that truly startling results have been obtained, results which the general public have qualified as marvelous . . .
>
> It may be objected that milk as a remedy is fairly well known and that every physician uses it according to the exigency of the case. I confess that all physicians are sufficiently informed regarding the virtue of milk, as food and as antidote, but I speak from experience when I say that in general the milk cure scrupulously administered in amounts rigorously fixed is not sufficiently, or but rarely, recognized by practitioners as an heroic and sovereign remedy.

Karell, who was physician to the Emperor of Russia, indulges in reminiscences of his excursion with the monarch through Russia, and speaks of his pleasure in seeing the milk cure being used extensively in many cases. He then transcribes a letter from the famous Niemeyer, which is worthy of being again transcribed. After having communi-

2. Karell: Arch. gén. de méd., 1866, viii, 513.

cated to the Tübingen professor his experiences, he received the following letter some time later:

> I am infinitely grateful to you for having recommended the milk cure; I have used it so often and extol it in such a way that it would make you smile. If one were sincere enough to recognize that there exists a very large number of disease whose cause should not be sought in disturbances of certain organs, but rather in a perverse state of nutrition, of which we know neither the extent nor the nature, he would believe in the curative virtue of milk, and would regard it as a true scientific advance that one can find in that article of food a harmless measure and at the same time so efficacious in changing completely the state of nutrition.

Karell has used the milk cure in at least 200 cases and found that it gave good results where other measures proved to be valueless. As to the principle underlying its virtues, he declines to give any opinion, and this he defends by claiming: "The art of healing would surely remain sterile if one should limit himself only to those remedies whose effects can be controlled even to the smallest detail." The diseases which are treated best by the cure are particularly dropsical conditions, but he gives a large list of other diseases of more or less chronic nature.

The writer has restricted himself to the employment of the Karell cure in cases of renal, cardiac and hepatic edema, and it is only these diseases which will be discussed in this paper, although other clinicians have used it in bronchitis, emphysema, gastric and intestinal conditions, and particularly in the treatment of obesity. Edema, from whatever cause is the condition, is par excellence the disease in which the most notable results are achieved, however.

ILLUSTRATIVE CASES

The following cases will illustrate the effect of the Karell cure in cases of edema:

Case 1.—John A., aged 70, white, was admitted to the hospital Feb. 11, 1914, complaining of dyspnea and edema of feet. A diagnosis of endocarditis and arteriosclerosis was made.

The patient states that he was fairly well until three years ago, when he became dyspneic and his feet began to swell. Since this time dyspnea has been pronounced on exertion; he has marked palpitation of the heart.

Examination revealed a well-nourished man; heart enlarged to right and to left; systolic murmur at apex and at aortic cartilage; extra systoles; vessels sclerotic; legs greatly swollen.

The urine had a specific gravity of 1.020, showed a trace of albumin, but no casts; blood: hemoglobin, 75 per cent.; leukocytes, 10,850; red blood cells, 4,970,000; blood pressure, systolic 212, diastolic 148.

Under treatment the patient regained fairly good condition and was discharged March 4, 1914. Edema had disappeared entirely, the subjective symptoms had much improved, and there was some reduction in blood pressure.

Case 2.—Frank P., aged 38, was admitted to the hospital Nov. 7, 1913, complaining of cardiac palpitation, dyspnea and edema of legs and scrotum. A diagnosis was made of aortic insufficiency and intermittent heart block.

The patient was well until two months ago, when, on returning home from work, he suddenly became very dyspneic. Similar attacks were of frequent occurrence after this.

It was learned that the patient had contracted syphilis and Neisserian infection at 28 years of age. He was treated in the Presbyterian Hospital two weeks ago for conditions similar to the present illness.

Examination showed him to be a poorly nourished man. Marked pallor and cyanosis were present and dyspnea pronounced; edema of legs and genitalia. Heart, apex beat was in the sixth interspace, 2 cm. outside left midclavicular line; right border at right parasternal line, left border 3 cm. to left of left midclavicular line. A systolic thrill was felt at the apex;; apex beat fluttering and diffuse. A presystolic murmur was heard at the apex, followed by a short diastolic murmur; double murmur at aortic and pulmonary cartilages. The liver was palpable. The lower extremities were edematous, as were also the penis and scrotum. The pulse was irregular and rapid, and the arteries sclerosed. While he was in the ward he had an attack of typical Stokes-Adams syndrome.

The urine had a specific gravity of 1.015, was cloudy, showed albumin, but no casts.

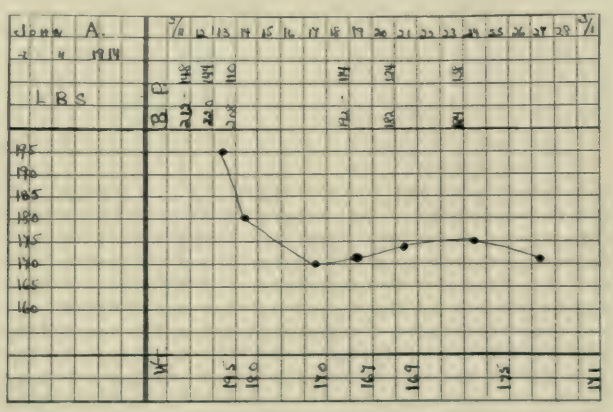


Fig. 1 (Case of John A.).—Line with heavy dots indicates loss of body weight, amounting to 26 pounds in ten days.

Blood: hemoglobin, 58 per cent.; red blood corpuscles, 3,280,000; leukocytes, 6,400; blood pressure, systolic 205, diastolic, 115.

Under treatment the patient lost in weight 8 pounds in seventeen days. Nine days after beginning Karell cure edema had almost entirely disappeared, and there had been a loss of weight of 15 pounds. Subjective symptoms had improved, and there were no sharp attacks of dyspnea, such as were complained of on admission, although patient was still dyspneic. The heart was more regular, pulse less frequent, no change in blood pressure. The patient was discharged Nov. 28, 1913, much improved.

Figure 2 shows loss of weight only, as the urine was not saved quantitatively and therefore is not recorded. Prognosis in this case was grave, although there was benefit from the Karell cure. The patient returned Dec. 29, 1913, with symptoms similar to those on his previous admissions. The Karell cure was again prescribed, but there was no improvement. Cardiac stimulants were employed, but patient succumbed Jan. 6, 1914.

Case 3.—Frederick P., aged 63, the same patient discussed in Case 4, was readmitted to the hospital Nov. 30, 1915. He had been coming since his discharge to my dispensary, but the exertion proved to be too much, and ten days

after his discharge dyspnea became marked, and legs, penis and scrotum became edematous. The condition on admission was the same as was given in Case 2, and a diagnosis of cardiac renal disease was made.

Under treatment the loss of weight amounted to 22 pounds in thirteen days. There was again disappearance of all edema and great improvement in subjective symptoms.

Figure 3 merely shows loss of weight. No accurate record was kept of the amount of urine, as the patient stipulated before entering the hospital the second time that he should be allowed to go to the toilet room, so the urine could not be collected quantitatively, as was possible during the patient's first visit to the hospital.

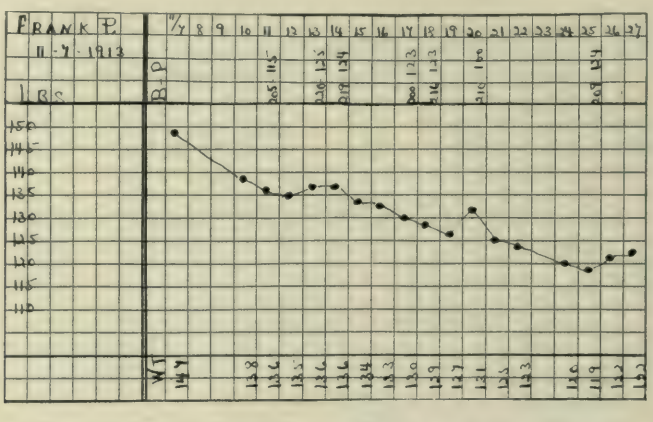


Fig. 2 (Case of Frank P.).—Line with heavy dots indicates the loss of body weight, amounting to 18 pounds in seventeen days.

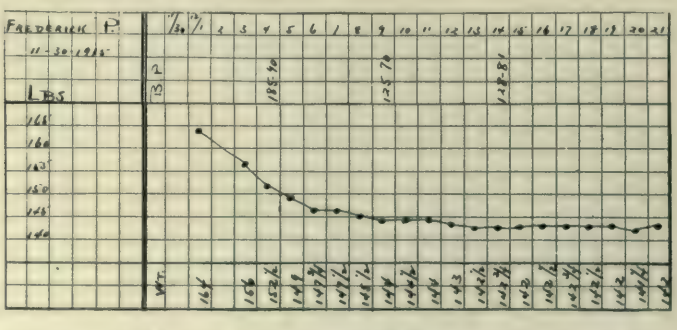


Fig. 3 (Case of Frederick P.).—Line with heavy dots indicates loss of body weight, amounting to 22 pounds in thirteen days.

Case 4.—Frederick P., aged 63, was admitted to the hospital Oct. 9, 1915, complaining of retention of urine and shortness of breath.

For two months the patient had had a smothering feeling at night, causing him to awaken with a start. It was observed that he became dyspneic on the slightest exertion and when walking he had to stop and rest after going the distance of a few hundred feet. He has had no polyuria and no other symptoms worth noting, except that after Sept. 3, 1915, a month previous to admission, he had become very weak.

He had been a sufferer from asthma previously, and a year ago he had a nasal operation which failed to furnish relief. His other history was negative.

Examination showed the patient to be a well-built man, complexion pasty; dorsal decubitus, but the slightest exertion causes dyspnea; face edematous; some hydrothorax both sides. The heart apex was in the sixth interspace to left of the midclavicular line. There was marked pulsation in the fourth and fifth left intercostal spaces. The right border was 4 cm. to right of midsternal line; left border 15 cm. to left of midsternal line. There was no murmur at apex, and the sounds were weak. The second sound at pulmonary and aortic cartilages was accentuated. There was marked edema of the entire body, and the abdomen showed ascites. The legs, scrotum and penis were very edematous; arteries sclerotic; catheterization required; eye grounds negative.

The urine was 1.013, albumin a faint trace, with hyaline and granular casts; phenolsulphonephthalein, 7 per cent.

Blood: Hemoglobin, 84 (?) per cent.; red blood corpuscles, 2,450.000 (?); leukocytes, 5,350; blood pressure: systolic, 169; diastolic, 110.

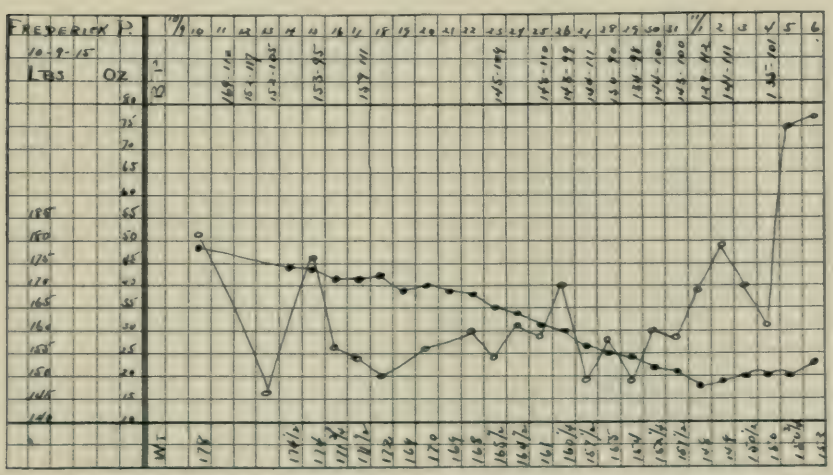


Fig. 4.—Same patient whose record is illustrated in Figure 3. The line with heavy dots indicates loss of body weight; line with open dots indicates amount of urine secreted, which rapidly increased at first, and then fell off, providing an indication for other therapeutic measures.

Under treatment there was a disappearance of the edema, and an improvement of subjective symptoms. The loss of weight was gradual, but amounted to 30 pounds in thirty days. There was a reduction of blood pressure. In this case hot packs were used and caffein 0.36 gm. a day. The patient was discharged Nov. 6, 1915.

Figure 4 shows marked increase in the amount of urine with later a falling off in quantity. On October 12 because of this, hot packs and caffein were ordered; later, digitalis, 2 c.c. of the tincture daily.

Case 5.—Ferdinand S., white, aged 61, was admitted to the hospital Jan. 12, 1914, complaining of dyspnea and swelling of the lower extremities. His case was diagnosed as cardiorenal.

His illness had begun six months before with shortness of breath, dizziness, and swelling of the feet and legs. Thereafter these symptoms had become intensified, until the patient could scarcely get his breath when he made even the

slightest exertion. His previous medical history showed pneumonia ten years before, and acute articular rheumatism two years before.

Examination showed a well-nourished man with marked dyspnea. There was chronic passive congestion at the base of the lungs. The heart sounds weak but regular, with no murmurs, and slight enlargement to the left. Ascites was present, the liver was palpable, and the lower extremities were edematous.

The urine was 1.029, with a trace of albumin, and with a few hyaline and granular casts at times.

Blood: Hemoglobin, 70 per cent.; red blood corpuscles, 4,800,000; leukocytes, 7,950; blood pressure: systolic, 190, diastolic, 140.

Under treatment there was a fall in body weight, and gradual increase in diuresis. Until Jan. 19, 1914, patient felt no better, but at this time he was improved, and the blood pressure, body weight and edema were all diminished. The patient was discharged Feb. 10, 1914, much improved.

Figure 5 shows the drop in body weight, the sudden diuresis, followed by a fall. The urine was not accurately measured for forty-eight hours, January 16 and 17. Then there was again an increase in amount, and a gradual fall in blood pressure.

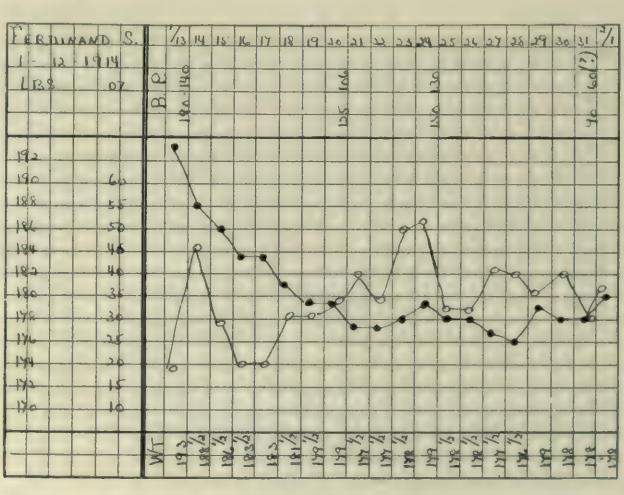


Fig. 5 (Case of Ferdinand S.).—Line with heavy dots indicates loss of body weight, which was 16 pounds in eight days; line with open dots, increase of diuresis.

Case 6.—Benedict P., aged 28, was admitted to the hospital July 10, 1913, complaining of dyspnea, distention of abdomen, edema of legs. His trouble was diagnosed as chronic nephritis.

His illness had begun six months before, when the patient noticed that his feet were swollen and he was unable to walk without becoming much fatigued. Two weeks before entrance edema became worse and dyspnea appeared.

Examination showed nutrition good. There were anasarca, ascites, and edema of the lungs. The heart apex was in the fifth midclavicular line, right border indefinite, left border in left midclavicular line. The sounds were indistinct, and there were no murmurs. There was no enlargement of the spleen or liver. The eye grounds were negative.

The urine was 1.018, heavy cloud albumin, and hyaline and granular casts; phenolsulphonephthalein 18 per cent.

Blood: Hemoglobin, 53 per cent.; red blood cells, 2,680,000; leukocytes, 9,900; blood pressure: systolic, 129; diastolic, 80.

Under treatment there was a loss of weight of 26 pounds in fourteen days. There was slight increase in urine excretion, and the edema became much less, although it was not entirely gone on discharge. There was a disappearance of all subjective symptoms, and a marked increase in chlorid output. The patient was discharged Aug. 27, 1913, much improved.

Figure 6 is designed to show loss of weight and delayed diuresis.

CASE 7.—Mary S., aged 57, was admitted to the hospital Oct. 7, 1914, complaining of shortness of breath, swelling of the legs and distention of the abdomen. A diagnosis of cardiorenal disease was made.

The patient had been suffering with edema of the legs for about a year or more, but she had became worse about five weeks before entrance to the hospital. The trouble had begun with abdominal distention, then dyspnea appeared, which became so pronounced that she could not lie down. She had been forced to sleep in her chair. Palpitation of the heart was marked, and there was blood-tinged expectoration.

The previous medical history showed rheumatism at the age of 16.

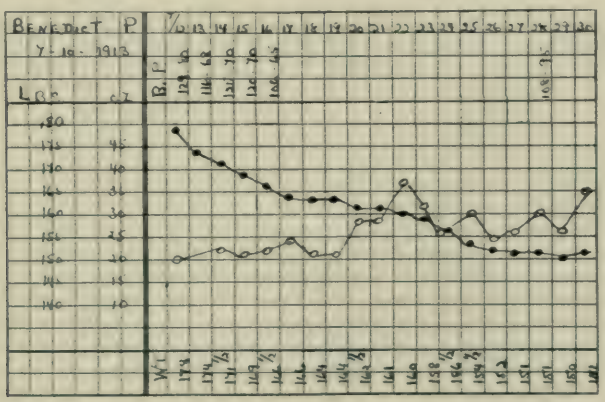


Fig. 6 (Case of Benedict P.).—Line with heavy dots shows loss of body weight, amounting to 26 pounds in fourteen days; line with open dots shows increase of diuresis, which was delayed in this case.

Examination showed the patient to be fairly well nourished, but very edematous. Pallor was present. The heart was irregular, and there was enlargement to the left and to the right, with a systolic murmur at the base. The arteries were sclerotic. The liver was palpable, and there were ascites, and marked edema of legs.

The urine was 1.016, with a trace of albumin and with hyaline and granular casts.

Blood: Hemoglobin, 60 per cent.; red blood cells, 3,640,000; leukocytes, 7,600; blood pressure: systolic, 145; diastolic, 90.

Under treatment there was a disappearance of all edema and a loss of weight of 54 pounds in ten days. The blood pressure was reduced from 145 systolic and 90 diastolic to 125 systolic and 80 diastolic in seven days.

Figure 7 shows the rapid loss of weight and the great diuresis, amounting to 4,500 c.c. On the second day of treatment the urine was 100 ounces, on third day 148 ounces, fourth day 138 ounces, fifth day 145, or a total of almost 16 liters (15,940 c.c.) in five days.

CASE 8.—Edward R., aged 35, was admitted to the hospital Jan. 12, 1914, complaining of "asthma," dyspnea, and swelling of the feet, legs and abdomen. The case was diagnosed as hepatic cirrhosis.

The patient had had shortness of breath for a number of years, but during the past six weeks he had been worse, and at the time of entrance was forced to rest sitting up. Cough had become very troublesome.

With the exception of asthma, patient had never been sick, but had been in the University Hospital in 1905 for some gastric trouble. He had always taken alcohol to excess; admitted Neisserian infection but denied syphilis.

Examination showed the patient to be a large, well-built man; semirecumbent decubitus. The breathing was labored and wheezing. There was pallor, and the lungs were emphysematous, with sibilant râles. The apex heart beat was not visible, the sounds were weak, and there was a soft systolic murmur at the apex. The area was not enlarged. There was abdominal ascites. The liver was palpable, and there was edema of feet and legs.

The urine was negative; phenolsulphonephthalein, 66 per cent. Gastric analysis showed total acid 8; free hydrochloric acid 0. Stools revealed occult blood present.

Blood: Hemoglobin, 45 per cent.; red blood cells, 3,390,000; leukocytes, 10,600; blood pressure: systolic, 120; diastolic, 70.

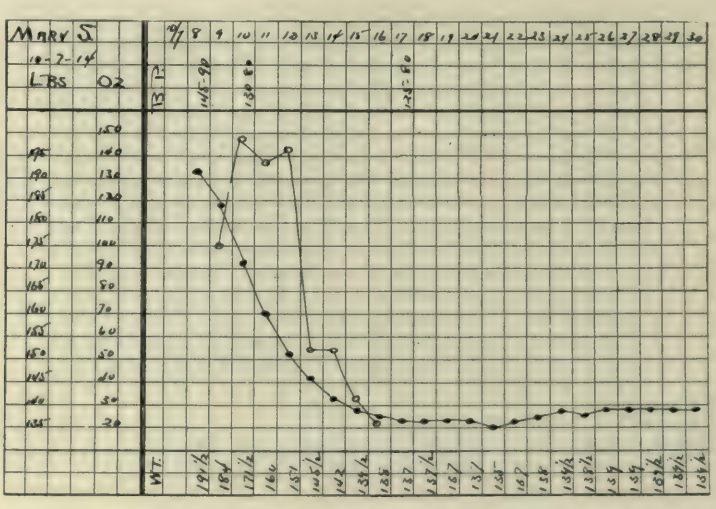


Fig. 7 (Case of Mary S.).—Line with heavy dots shows loss of body weight, which was 54 pounds in ten days; line with open dots shows rapid increase of diuresis, 531 ounces of urine being secreted in four days.

Treatment produced a loss of weight of 39 pounds in sixteen days. The diet was increased on the seventh day of treatment. The patient was improved when discharged, Feb. 26, 1914.

Figure 8 shows a rapid loss of weight and a prompt increase in the amount of urine.

Case 9.—William W., aged 22, was admitted to the hospital Nov. 4, 1913, complaining of dyspnea, cough and expectoration, pain on inspiration, scanty urination, swelling of feet, and ascites. The case was diagnosed as endocarditis; decompensation.

The patient had never been sick with a similar illness. He had been apparently well and walking about until two weeks before admittance, when he began to notice swelling of the feet, and began to lose his appetite. He also developed a severe pain in the right infraclavicular region, sharp, stabbing in character, made worse by taking a deep breath, and on coughing, which soon developed. He became dyspneic on exertion. For the past two weeks

he had been passing but little urine, which was dark in color. There was pain in back over the renal region. The face had started to swell about two weeks previously, and about that time he noticed that his abdomen had become swollen.

His previous medical history was negative. He was in the habit of using alcohol to excess and of doing hard work.

Examination showed a well-nourished young man. He had a uremic odor to the breath; face swollen and flushed; dyspneic. The abdomen was swollen, the lungs tuberculous, with pleural effusion. The apex heart beat was in the sixth interspace, 14 cm. to the left of the midsternal line; upper border at the third rib, right border 4½ cm., left border 14 cm. from midsternum. The sounds were irregular, gallop rhythm, systolic murmur at the apex. The abdomen showed ascites. The liver was palpable and pulsating. The lower and upper extremities were edematous.

The urine was 1.080 with heavy cloud albumin and no casts.

Blood: Red blood cells, 4,710,000; leukocytes, 18,150; blood pressure: systolic, 131; diastolic, 93.

As a result of treatment, on November 10 the patient seemed a little better, was not so dyspneic, but began to be jaundiced. Later, Nov. 19, 1913, there was parencentesis thoracis. Patient gradually became worse and despite active use of cardiac stimulants, succumbed on Nov. 28, 1913.

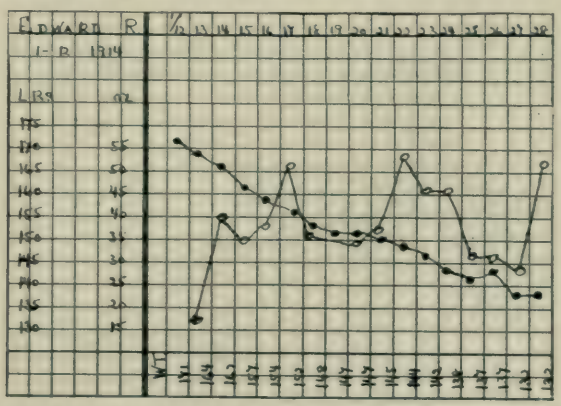


Fig. 8 (Case of Edward R.).—Shows effect of the milk diet in a case of hepatic cirrhosis. The line with heavy dots indicates the loss of body weight, which was 39 pounds in sixteen days; line with open dots shows the increase in diuresis.

Figure 9 shows only moderate loss of weight very slowly achieved, with urine amounts continually low. There was no improvement in pulse rate. The prognosis on admission was guarded.

Case 10.—James K., aged 49, white, was admitted to the hospital Sept. 2, 1913, complaining of swelling of legs, genitalia and abdomen. A diagnosis of chronic nephritis was made.

The patient had been well until five weeks before, when he noticed that he was beginning to tire easily, had general malaise and was losing appetite. One week before he had first observed swelling in the face, and the next day general swelling throughout the body. He had had diarrhea one week before, soreness across the abdomen, pain in the back and polyuria. Three weeks before he had had pains about the heart which had lasted for three days and prevented him from taking full breath. Dyspnea and palpitation also were complained of.

He had had nephritis with dropsy eighteen years before, and had been treated in the Presbyterian Hospital and discharged as cured.

Examination showed a well-nourished man. There was slight cyanosis, the face was puffy and the breath urinous. A few moist râles could be detected at the base of both lungs. The right border of the heart was 2 cm., the left border 12 cm. to the left of the midsternal line. The upper border

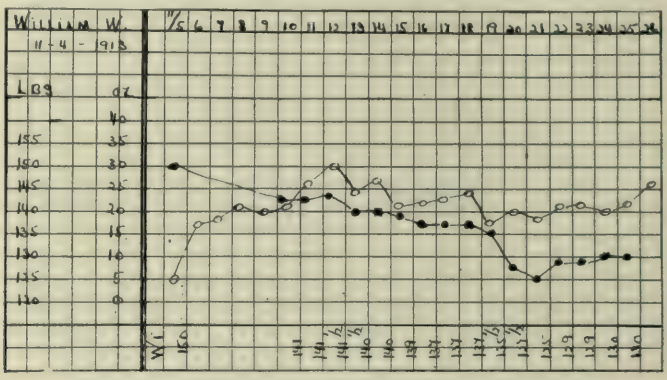


Fig. 9 (Case of William W.).—Illustrates failure of the Karell cure; slow and halting loss of body weight indicated by the line with heavy dots, and very small amounts of urine, indicated by the line with open dots, the largest amount being but 30 ounces.

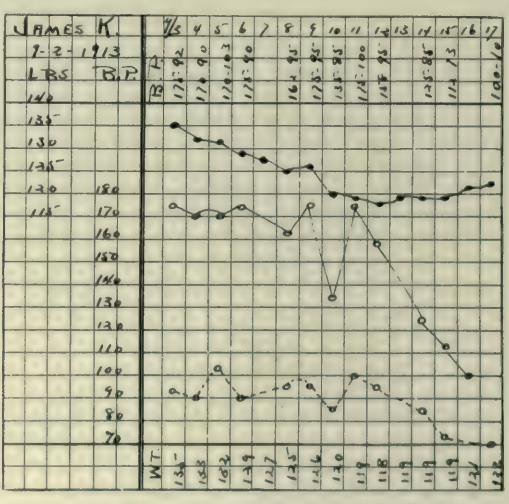


Fig. 10 (Case of James K.).—Shows chiefly the lowering of blood pressure, both systolic and diastolic, due to Karell diet. Line with heavy dots indicates loss of body weight; solid line with open dots indicates the systolic blood pressure, and broken line with open dots, diastolic blood pressure.

was at the third rib. The first sound at the mitral area was roughened and prolonged. The pulse was regular. The arteries were sclerotic, the urine showed many hyaline casts, and edema was general.

The urine was 1.010, with a heavy cloud albumin and many hyaline casts, and phenolsulphonephthalein excretion of 40 per cent.

Blood: hemoglobin, 60 per cent.; red blood cells, 4,570,000; leukocytes, 11,200; blood pressure: systolic, 175; diastolic, 92.

Under treatment there was a loss of 16 pounds of edema in eight days, with disappearance of all swelling. Diuresis increased, but it has not been charted as the amount was not accurately measured. There was a gradual fall in blood pressure, systolic and diastolic, and a disappearance of all subjective symptoms. The patient was discharged Sept. 17, 1913, much improved.

Figure 10 is designed to show the loss of weight and decrease of blood pressure.

Case 11.—Margaret McC., aged 37, was admitted to the hospital Feb. 23, 1910, complaining of edema of face, abdomen, extremities, and of pains in the back. Her trouble was diagnosed as nephritis.

Two weeks before she had noticed puffiness about the eyes, most marked in the mornings. In a few days her feet had become swollen, and later her hands. The swelling had increased each day, and finally the abdomen had become involved in the edematous process.

Her previous medical history showed that she had had scarlet fever.

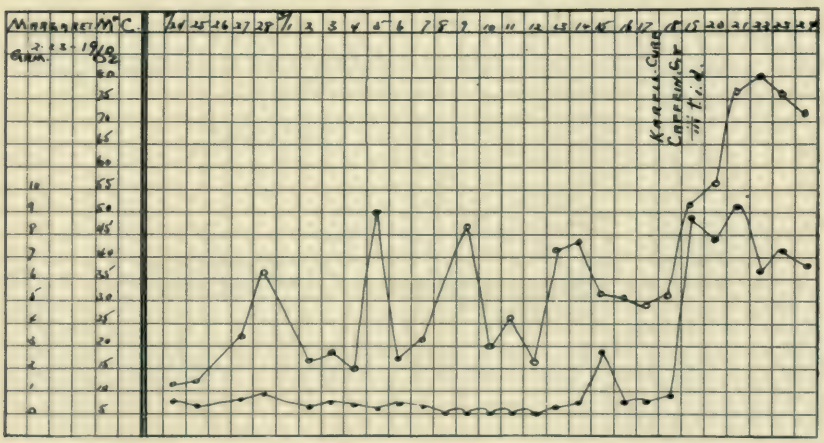


Fig. 11 (Case of Margaret McC.).—Shows retention of chlorids on a solid salt-poor diet; prompt elimination of chlorids and increased diuresis on Karell cure, with caffein and hot packs. Line with heavy dots indicates body weight; line with open dots shows the effect of the Karell treatment on diuresis.

Examination revealed slight edema of the face, heart enlarged to the left, with a soft, low-pitched systolic murmur at the apex. No ascites. Extremities edematous.

The urine was 1.016, with a small amount of albumin and few fine granular and hyaline casts.

The blood pressure was 125 systolic and 100 diastolic.

In the treatment salt-free diet was used, but not the Karell cure. On January 19, owing to signs of impending uremia, a Karell diet with hot packs and caffein 0.2 gm. three times a day were ordered, and the result was improvement in the urine, the chlorids and in the patient's general condition.

Figure 11 shows absolute chlorid retention despite increasing amount of urine, and the prompt and rapid elimination of chlorids and marked diuresis on combination Karell diet and medication.

Case 12.—Elizabeth W., aged 36, was admitted to the hospital Feb. 12, 1910, complaining of edema of extremities and abdomen. Her case was diagnosed as nephritis.

Three weeks before, the patient had noticed slight swelling in the feet at night, the edema disappearing by morning, and puffiness about the eyes had appeared at the same time. The swelling had gradually increased, the entire body had become edematous. During the summer of 1909 the patient had noticed some swelling in her feet which disappeared in a few days.

Examination showed anasarca, heart not enlarged, accentuation of both pulmonic and aortic second sounds and no retinitis.

The urine was 1.013, with large amounts of albumin and hyaline and granular casts.

Under treatment there was a rapid loss of weight and disappearance of edema. The patient was discharged much improved.

Figure 12 illustrates the great loss in body weight, increase in urine, and marked chlorid elimination.

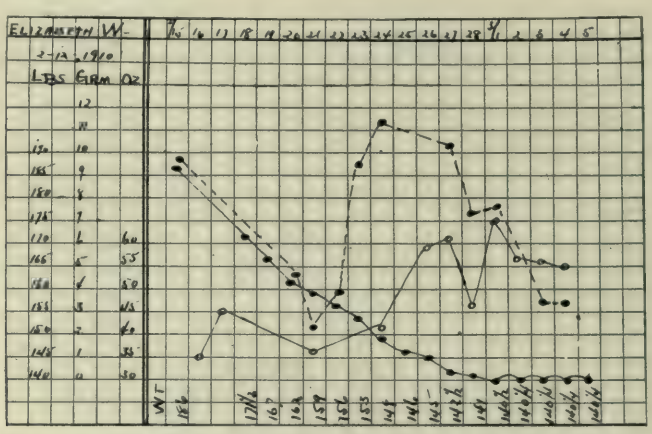


Fig. 12 (Case of Elizabeth W.).—Solid line with heavy dots indicates loss of body weight, which was 30 pounds in fourteen days. Broken line with heavy dots shows the elimination of chlorids, and the line with open dots the increase of urine excretion.

EFFECT OF THE CURE

1. *Subjective State.*—The most important feature of the cure is that it gives the human organism the minimum of work. All strain on the heart is removed as far as is possible by the rest in bed and by the very small amount of food given at frequent intervals, which yet furnishes enough nutrition under the circumstances and provides fuel in such a form that it can be utilized with the least possible effort. The good effects are seen by the patient almost before they are noted by the physician. The patient rests easier, there is a gradual cessation of subjective symptoms, headache, depression, vertigo, and there is a return of the desire to partake of food where formerly nausea and vomiting held sway. There is an improvement in the respiratory condition, and the patient has less dyspnea, requires fewer pillows for his comfort, gradually assumes the prone position, and is able to have long sleep without the intervention of morphin. These favorable changes are the reward of the strict observance of the Karell cure,

and the strict observance consists in giving only 200 c.c. of milk at 8 a. m., 12 m., 4 p. m., and 8 p. m. The purpose of the treatment is immediately defeated if more fluid is permitted or if the patient is allowed to drink the milk whenever he pleases.

2. *Heart.*—The effect on the heart is soon noticed apart from the subjective symptoms of restored compensation. Good effects are seen more constantly in those cases which are best termed myodegeneratio cordis, that type of cardiac disease seen in senility, emphysema, chronic alcoholism and in cachectic states (Wittich). In 60 per cent. of this type of case improvement is seen. Valvular disease is improved in about 43 per cent. of cases, arteriosclerosis in 33 per cent., and according to Wittich, in nephritis only 14 per cent., a percentage below that seen in my cases. Under the combination of rest in bed and the Karell diet the pulse assumes, first, a better quality, and later becomes less irregular and less frequent. These effects are seen in many cases in which no medication is used, although we do not presume to deny the place digitalis preparations have earned for themselves in the treatment of arrhythmia and allorhythmia. In some cases digitalis preparations must be used, but their action is materially reinforced by the use of the milk cure.

3. *Blood pressure* is generally lowered, particularly in cases of renal hypertension, as may be seen from Figure 10.

4. *Urine.*—When the daily quantity of urine is closely watched it will be seen that there is marked increase in the amount. This in some cases begins within the first few days and reaches its height during the first week (Fig. 7), but in other cases diuresis is delayed (Figs. 4 and 12). Most authors state that the largest amounts are seen in the first two to three days, but this has not been the rule in my cases. At times there is a delayed diuresis, as has been described by His. The urine passed in twenty-four hours may be two or three times the amount of milk ingested, 5 liters having been observed. In the case of Mary S. (Case 7), almost 4,500 c.c. were voided, and in this patient there was a loss of weight of 54 pounds in ten days. The specific gravity of the urine is variable, but generally speaking, it is in inverse ratio to the amount of urine excreted. On the other hand, there has been noted a distinct rise in specific gravity without any change in the amount. The quantity of albumin diminishes and disappears when there is chronic passive congestion, and there is also a reduction in the number of casts, although this is not so apparent when a true nephritis is present. The effect on the phenolsulphonephthalein output is variable, but it can not be said that there is any marked increase in the amount excreted.

5. *The chlorid output* is generally very much increased over the intake. Repeated analyses by Hegler have given the percentage of

salt in milk as 0.14, which would be about 1.1 gm. in 800 c.c. milk. By reference to Figure 12 it may be seen what relation the output bears to the intake. Wittich regards this negative chlorid balance as a good indication of the efficacy of the treatment, and attaches greater importance to it than to the twenty-four-hour quantity of urine in estimating the changes in the circulatory apparatus. Ordinarily there is a marked increase in the amount of sodium chlorid during the first few days, both as to percentage and total amount. After two or three days the percentage falls, but the total amount increases, with the increase in urine, and finally, as the urine amount returns to normal, the chlorid balance is regained (Wittich).

TO WHAT IS IMPROVEMENT DUE?

An attempt has been made to ascribe the benefits following the Karell cure to three factors, namely, reduction in the amount of fluid, the minimum of salt contained in the milk, and finally to the melting of body protein. The last-named factor has probably some bearing on the effect of the cure when carried out in obese patients, but is scarcely to be considered as a factor in the cases of edema in which as much as 31 pounds have been lost in three days (Mary S., Fig. 7). Hence, in the cases studied as a basis for this paper the so-called melting of body protein hardly calls for consideration.

Metabolic studies have been made by Hegler on patients suffering with renal or cardiac decompensation or both, associated with obesity. He does not consider that the limited amount of fluid ingested alone accounts for the diuresis and loss of weight, and this he proves by a patient who took 800 c.c. of milk and a liter of infusion of lime tree blossoms, and who nevertheless lost 10 kg. weight in eight days.

To the low salt content of the diet has been ascribed much of the benefit resulting from the cure. During the first three or four days of the cure patients excrete daily 8, 10 or 15 gm., or even more, of sodium chlorid; but after from five to eight days the excretion of this salt sinks to from 1 to 2 gm. per day and when a diet containing from 1 to 3 gm. of sodium chlorid is given, there is a transitory tendency to sodium chlorid retention. If the sodium chlorid equilibrium is followed for a longer period of time, there is always a preponderance of sodium chlorid excreted over that ingested, as much as from 40 to 60 gm. in from three to four weeks. This is in contradistinction to Hedinger, who found a considerable sodium chlorid retention and water retention, which, to his mind, accounted for the rapid gain in weight after completion of the cure (obese cases?). Hegler has made the interesting observation that sodium chlorid added to the diet of an obesity case causes no water retention and no gain in weight; but when the same experiment is tried in dropsical individuals, there is an immediate cessa-

tion of loss in weight, with water and sodium chlorid retention, and finally gain in weight. This latter experiment is by no means new, however, and was first performed by Javal and Widal. Somewhat similar results were also obtained by v. Hoesslin in normal individuals.

From this it would seem that the good effects might be ascribed to the sodium chlorid poverty of the diet, but here again we find contradiction in a case described by Wittich.

TABLE 1.—Showing Diuresis and Sodium Chlorid Output as Affected by Karell Treatment (Wittich's Patient)

Date, 1911	Diet	Urine	Sodium Chlorid in Grams	
			Intake	Output
May 28	Salt-free diet without limiting fluid	700	3	4.2
May 29	Salt-free diet without limiting fluid	700	3	3.5
May 30	Karell cure	1,400	1.7	10.1
May 31	Karell cure	1,300	1.7	9.2
June 1	Karell cure	800	1.7	4.4

Wittich's patient, as shown in Table 1, received for two days a salt-poor diet, but was allowed as much fluid as he desired. There was no increase in diuresis, however; but as soon as the Karell diet was given, although now but 800 c.c. of fluid was permitted, the amount of urine was doubled. It is difficult to see just how a reduction of sodium chlorid intake (1.3 gm. less than on the salt-poor diet) could account for the increase in urine and the remarkable increase in the amount of sodium chlorid excretion.

It appears more probable that there are several factors which account for the efficiency of the Karell diet: (1) absolute rest in bed, which removes from the organism practically all work, and decreases the amount of work to be borne by the heart; (2) the low amount of fluid and food (800 c.c., containing only 27 gm. protein and furnishing about 520 calories) also limits the amount of cardiac effort; (3) the low amount of sodium chlorid; and finally (4) the effect of the Karell cure may be due to either the salt-poor diet or to the low amount of fluid, or it may be the sum of the two, which brings about the brilliant results.

Hegler, as a result of his metabolic studies, decides that the value of the Karell cure can not be judged from such studies, but must be estimated from the clinical side, and I would here call attention to Karell's remark previously quoted. No matter to what factor or factors the good results are ascribed the fact remains that in dropsical

conditions of renal, cardiac and perhaps hepatic origin the Karell milk diet, given as taught by Karell, is the diet par excellence.

THE USE OF DRUGS IN COMBINATION WITH THE KARELL CURE

In pursuing my studies the object has been to use only the Karell cure itself and to avoid as far as possible any medication. In many cases the milk diet alone brings about the desired improvement and no drugs are necessary, but in other cases medicines can not be dispensed with. It has been noted frequently that patients who have been treated for a period of time with digitalis preparations without much improvement do particularly well on the Karell diet alone. On the other hand, cases presenting marked dyspnea, cyanosis, a frequent and irregular pulse, need relief more rapidly than is possible with the Karell cure by itself. Such drugs as camphor, digitalis, strophanthus, caffein and morphin should be used in such emergencies, but it will be found unnecessary in the majority of cases to continue with their administration for any great length of time. Generally at the expiration of twenty-four or forty-eight hours there has been such a marked improvement that they may be discontinued.

When the Karell cure has been used for a few days, and when there has been no objective improvement, that is, when the quantity of urine becomes markedly decreased, when there is no change in the character of the pulse, and when the body weight and the edema remain as before, or when both increase, then drugs must be used. Of these, digitalis, theocin, caffein and strophanthin seem to be especially suitable, and an observation of Jacob's is worthy of repetition, namely, that whereas in these cases digitalis preparations alone, even in large doses, have had but little effect on the decompensated heart, when used with the Karell cure a much better result is seen, and much smaller doses of digitalis are required. This is especially to be seen when digitalis has been discontinued for a few days before beginning again with their administration.

PROGNOSTIC SIGNIFICANCE OF THE KARELL CURE

Jacob, Wittich and others have called attention to the prognostic significance to the pure Karell cure, or the Karell cure used without medication. Wittich especially regards the prognosis as serious when there is chlorid equilibrium, persistence of edema, and stationary urinary output or a diminution of the same, but particularly important is the chlorid output, by means of which one is enabled to decide on the prognosis by the first day. A positive chlorid balance is absolutely unfavorable, and in his case this was seen in but two cases, and these patients died within the first few days of the cure. Wittich also claims to see in the chlorid metabolism not only an index of the extent

of reestablished compensation, but also of beginning compensation following a Karell cure. When at the end of a Karell cure there begins to be salt retention, he regards this as an early sign of a fresh decompensatory state—a preedematous stage of cardiac decompensation—and he recommends a repetition of the Karell cure in order to spare the heart any further fatigue.

In 1910 I called attention to the unfavorable significance of this chlorid retention, and a chart published at that time is reproduced here (Fig. 11). This patient was not on the Karell diet, but was given what is popularly called a salt-free diet, but more properly, a salt-poor diet.

CONTRAINDICATIONS

During our experiences with the Karell cure there have been no bad results when the treatment has been properly used. There are cases, however, which do not seem to respond to the diet, and for this reason the Kareli treatment is no longer recommended in these instances. Patients exhibiting symptoms of uremia should not be put on the Karell cure, which restricts the fluid intake to a minimum, as it has been shown by Senator and others that in this crisis the fluid intake should be greatly augmented for the purpose of flooding from the system the unknown toxic substance or substances believed to be the causative factor in uremia. Wittich states that the Karell cure in two cases of uremia left him absolutely in the lurch, and the patients were made materially worse. The treatment of such individuals should be that well known to all practitioners of medicine, and the Karell cure has no place whatever in the management of such cases.

248 South Twenty-First Street.

ON THE REACTION OF THE CEREBROSPINAL FLUID*

S. H. HURWITZ, M.D., AND C. L. TRANTER, M.D.
SAN FRANCISCO

In its mode of origin and in its pathways of absorption, as well as in its physical and chemical properties, the cerebrospinal fluid is unique among the body fluids. Two facts derived from clinical and experimental observations have been established within recent years with a fair degree of conclusiveness, namely, the dual origin of the cerebrospinal fluid and its return to the general circulation chiefly by a process of filtration through the arachnoid villi into the great sinuses.[1, 2] Unlike the circulating lymph, which is derived from the blood by a process of filtration, diffusion and osmosis, the cerebrospinal fluid is the secretory product of the ependymal cells which cover the choroid plexuses, although it must be admitted that certain fundamental anatomic and physiologic aspects of this problem are still unsolved.

Another interesting observation which has been brought forth by a number of workers is that these plexuses constitute a remarkably effective barrier against the entry into the cerebrospinal fluid of substances present in the circulating blood. This observation may indeed explain, in part at least, the unique physical and chemical properties of the fluid, for in these respects also it is unlike any other fluid in the body, being approached in its composition most nearly by the sweat, tears, and aqueous humor of the eye. From the circulating lymph normal cerebrospinal fluid differs in several striking particulars: it is of lower specific gravity, contains a small content of salt, only minute traces of protein, and no fibrinogen.

Concerning the reaction of the cerebrospinal fluid, little more definite is known beyond the general statement of most authors that it is alkaline. As to the degree of this alkalinity in comparison to the other body fluids and more especially to the blood little is known. According to Cavazzani—and most authors quote him—the alkalinity of the fluid is only half as great as that of the blood.[2, 3] Mott has attempted to express the degrees of reaction in terms of percentages of

* Submitted for publication April 6, 1916.

* From the George Williams Hooper Foundation for Medical Research, and the Neurologic Clinic, the University of California Medical School, San Francisco.

1. Weed, Lewis H.: Jour. Med. Research, 1914, xxxi, 21, 51, 93.
2. Mott, F. W.: Lancet, London, 1910, ii, 1, 79.
3. Plaut, F.; Rehm, O., and Schottmüller, H.: Leitfaden zur Untersuchung der Zerebrospinalflüssigkeit, Jena, Gustav Fischer, 1913, pp. 16, 23.

sodium hydroxid. Calculated in this way, the reaction has been found by him to vary only slightly in different animals, and in man in different pathologic conditions. On an average it corresponds to 0.1 per cent. sodium hydroxid.

That such titrimetric determinations of reaction lack accuracy has been repeatedly emphasized in recent literature.[4, 5] The more extensive knowledge gained from modern physicochemical studies has shown that the titrimetric method in its present form is inaccurate, and that an exact knowledge of the reaction of a solution can be gained only from a determination of its hydrogen ion concentration.

Although extensive studies have been made of the hydrogen ion concentration of most biologic fluids, electrometrically or by the colorimetric method, we were surprised to find almost no mention in the literature of similar determinations on the cerebrospinal fluid. Neither Sörensen[6] nor Michaelis[7] in their exhaustive treatises on this subject make any reference to such studies.

So far as we are aware, Polanyi, quoted by Bisgaard,[8] was the first to determine the hydrogen ion concentration of the spinal fluid. He found the value for pH to be 10.04 (9.08×10^{-11}). Bisgaard, however, who carried out similar determinations both by the gas-chain electrometric method, as well as colorimetrically, gives the value as 8.10, although fluids obtained post mortem were found by him to be more alkaline (pH=8.46 to 9.25). This worker found also that the results obtained by the Hasselbach apparatus corresponded well with those obtained colorimetrically with phenolphthalein as indicator.

In view of the meagerness of data on this point, it seemed worth while to determine the hydrogen ion concentration of normal cerebrospinal fluid, as well as of fluid obtained from patients suffering from several types of disease. In the present paper we wish to report the results of such determinations made by the colorimetric method upon forty-seven fluids.

METHOD

Sources of Error.—In a recent communication[5] we presented in some detail the principles and the extent of applicability of the colorimetric method for determining the hydrogen ion concentration of bio-

4. Clark, W. M.: Jour. Infect. Dis., 1915, xvii, 109.

5. Hurwitz, S. H.; Meyer, K. F., and Ostenberg, Z.: Bull. Johns Hopkins Hosp., 1916, xxvii, 16.

6. Sörensen, S. P. L.; Ergeb. d. Physiol., 1912, xii, 393.

7. Michaelis, Leonor: Die Wasserstoffionenkonzentration, Berlin, Julius Springer, 1914.

8. Bisgaard, A.: Biochem. Ztschr., 1913-1914, lviii, 1.

logic fluids, but only brief reference was then made to the sources of error of the method. These in the main are three in number,[9] and a critical analysis of them will show that they do not materially alter the accuracy of the method in its application to cerebrospinal fluid.

1. The Effect of Coloring Matter in Biologic Fluids: One of the greatest obstacles met with in the use of colorimetry in the determination of the ionization of biologic fluids is the turbidity and the pigment present in the majority of such fluids. In the case of blood this difficulty was unsurmountable until Levy, Rowntree and Marriott[10] suggested the method of determining the ionization of the dialysate obtained by dialyzing blood through collodion membranes for a given time interval. It is obvious that this difficulty does not arise in the case of cerebrospinal fluid, which, in health and when carefully obtained without contamination with blood, is usually a colorless, limpid fluid. Should any turbidity exist due to the presence of inflammatory products, the fluid can still be read directly by use of the comparator method described in a previous paper.

2. Influence of Neutral Salts: Those who have used this method are agreed that the presence of neutral salts in sufficient concentration greatly influences the point at which a given indicator changes color. In this respect various indicators show different degrees of sensitiveness. In most instances the neutral salt concentration must be two to three times that of blood in order to render the use of indicators for these determinations subject to gross error.[11] From the available analyses of the blood and the cerebrospinal fluid it would appear, how-

---

9. A source of error which should be mentioned, but which is not peculiar to any one method, is that which may result from the loss of carbon dioxid in determinations of hydrogen ion concentration on carbon-dioxid-containing fluids, such as blood and cerebrospinal fluid. The possibility of this error has been precluded in electrometric measurements by the use of a special electrode, the Hasselbach electrode, for the purpose of keeping the carbon dioxid tension at a constant level during the measurements. In the use of the colorimetric method this difficulty cannot be met with entire satisfaction, and the values for pH obtained do not in a strict sense have the absolute accuracy possessed by readings made with the hydrogen electrode. But it would appear from Mott's work[2] that the carbon dioxid in cerebrospinal fluid is in more stable combination than in blood, and for this reason this medium is more suited to colorimetric readings than is the blood. In every case it is important to make the determinations on perfectly fresh specimens and with a similar technic in order to give the results comparative value.

10. Levy, R. L., Rowntree, L. G., and Marriott, W. McKim: THE ARCHIVES INT. MED., 1915, xvi, 389.

11. Rona, P.: Handbuch d. Biochemische Arbeitsmethoden, E. Abderhalden, 1911, v, 321.

ever, that the inorganic salts exist in the two fluids in about equal concentration.[12]

3. Influence of Proteins and their Split Products: Because of their colloidal properties and their amphoteric character, proteins or their split products greatly modify the point at which certain indicators change color, and this quite independently of the hydrogen ion concentration. Their presence, therefore, constitutes a source of error which at times is sufficiently great to render the colorimetric method inapplicable to solutions containing protein in high concentration. From what has already been said concerning the extremely low protein content of normal cerebrospinal fluid, it is apparent that this source of error does not apply to it. According to Mott and others, normal cerebrospinal fluid contains only 0.03 per cent. of protein, and in pathologic cases it seldom exceeds 0.25 per cent.[3]

From the above considerations it is clear that because of the unique chemical composition of the cerebrospinal fluid colorimetric determinations of its ionization are not subject to the same sources of error which would arise in the case of other biologic fluids.

Technic.—The principles of the colorimetric method, the preparation of the standard comparison tubes and the manner of expressing the results are recorded in recent communications.[5, 10] In this paper it is necessary only to give the several steps in the procedure.

Spinal fluid is obtained by lumbar puncture in the usual way, and is received into thoroughly clean and dry Jena glass test tubes.[13] Because of the clear, watery nature of the fluid and its low protein content, it is possible to make the determinations of the hydrogen ion concentration either directly or indirectly by testing the dialysate as recommended for blood by Levy, Rowntree, and Marriott.

For a direct reading 3 c.c. of spinal fluid are delivered into a small clean and dry test tube 10 by 100 mm., and 0.3 c.c. of a 0.01 per cent. solution of phenolsulphonephthalein is added. After inverting the test tube several times in order to distribute the color evenly, comparisons are made between the color obtained and those of a series of standard

12. Gautier and Zdarek (quoted by C. E. Simon, Clinical Diagnosis, Ed. 8, Philadelphia, Lea & Febiger, 1914, p. 501) give the concentration of chlorids, phosphates and sulphates in cerebrospinal fluid as 6.44 per mille; while Hammarstern, O. (A Text Book of Physiological Chemistry, Ed. 8, New York, John Wiley & Sons, 1909, p. 239) states that the blood as a whole contains in ordinary cases from 770 to 820 per mille water, with from 180 to 230 per mille solids, of which from 6 to 10 per mille are inorganic and the remainder organic solids.

13. We have found that some of the thick-walled test tubes, even when thoroughly clean, deliver up alkali in sufficient amount to render distilled water placed in them alkaline to phenolsulphonephthalein. This source of error must of course be obviated.

TABLE 1.—THE HYDROGEN ION CONCENTRATION OF NORMAL CEREBROSPINAL FLUID

Number of Case	Date	Name	Age	Diagnosis	Hospital Number	Wassermann*	Cell Count	Nonne	Noguchi	Reaction of Cerebrospinal Fluid, Value of pH	Reaction of Spinal Fluid Dialysate, Value of pH	Reaction of Blood Dialysate, Value of pH	Remarks
1	8/17/15	S. R.	55	Tuberculosis of wrist....	15413	B. — S. F. —	3	0	0	8.3	8.3	....	
2	8/19/15	A. H.	50	Diabetes.....	16258	B. — S. F. —	2	0	0	8.25	8.15	....	
3	8/19/15	A. C.	63	Chronic nephritis.....	16593	B. — S. F. —	2	0	0	8.3	8.2	....	
4	8/24/15	C. B.	39	Paranoia.....	16509	B. — S. F. —	1	0	0	8.3	8.15	....	
5	8/24/15	J. G.	28	Sinusitis.....	12402	B. — S. F. —	2	0	0	8.3	8.15	....	
6	8/24/15 8/28/15	H. V.	7	Cerebral injury, decompression	House 9732	.....	2	0	0	8.15 8.3	8.0 8.15	....	Three spinal punctures with withdrawal of considerable fluid
7	8/26/15	P. P.	53	Pulmonary tuberculosis	11107	B. — S. F. —	2	0	0	8.3	8.1	....	
8	8/31/15	W. H. T.	58	Cerebral injury.....	House 9732	B. — S. F. —	2	0	0	8.15	8.05	....	
9	9/ 1/15	D. S.	56	Neurasthenia.....	14136	B. — S. F. —	0	0	0	8.25	8.2	7.7	
10	9/ 1/15	T. W.	45	Tabes (?).....	17108	B. — S. F. —	5	0	0	8.3	8.1	7.6	No positive clinical signs of tabes
11	9/21/15	J. S.	43	"Dizziness".....	17475	B. — S. F. —	3	0	0	8.3	8.15	7.75	
12	9/30/15	J. S.	54	History of syphilis.....	17578	B. — S. F. —	2	0	0	8.25	8.0	7.65	No signs or symptoms of syphilis
13	9/30/15	C. D.	45	Retinitis.....	15954	B. — S. F. —	2	0	0	8.3	7.95	....	
14	10/ 2/15	M. E.	20	History of syphilitic infection (?)	17915	B. — S. F. —	1	0	0	8.25	8.05	7.65	No signs of syphilis
15	10/ 7/15	T. E.	28	Papillitis.....	17765	B. — S. F. —	0	0	0	8.3	8.25	....	
16	10/ 7/15	A. B.	42	Tabes (?).....	.....	B. — S. F. —	0	0	0	....	8.25	....	No clinical signs of tabes
17	10/19/15	L. I.	42	Syphilis (?).....	18158	B. — S. F. —	0	0	0	8.3	8.0	....	
18	10/23/15	A. A.	45	Tabes (?).....	10283	B. — S. F. —	1	0	0	8.25	....	....	
19	12/ 8/15	T. B.	43	Syphilis (?).....	19291	B. — S. F. —	0	0	0	8.20	8.0	7.65	
Averages.....					.....	.....	...	...	...	8.26	8.11	7.66	

* B. means blood; S. F. means spinal fluid.

solutions consisting of phosphate mixtures prepared according to the directions of Sörensen.[14] The color in the standard series which most closely matches that of the solution tested gives the hydrogen ion concentration of the test fluid.

If it be desired to test the dialysate in order to compare its hydrogen ion concentration with the dialysate of the blood of the same patient, 1 to 2 c.c. of cerebrospinal fluid are placed into a collodion sac, which is then lowered into a small test tube containing 3 c.c. of physiologic salt solution, until the fluid on the outside of the sac is as high as that on the inside. Dialysis is allowed to continue for five minutes. The collodion sac is then removed, and 0.3 c.c. of the indicator solution is added to the dialysate. Color comparisons with the standard scale are now made as detailed above. For comparative purposes the same quantity of the same patient's blood is tested in a similar manner.

RESULTS

The Reaction of Normal Cerebrospinal Fluid.—In Table 1 have been grouped nineteen normal patients in whom the reaction of the cerebrospinal fluid was determined. These patients, as will appear, represent a large variety of clinical conditions, and in a strict sense cannot be classed as normal. But so far as the cytologic, chemical and serum tests indicate, no abnormality existed in the central nervous system, and on this ground it is justifiable to place them in the normal group.

It will be noted that in the nineteen determinations made upon the fluid directly the average value of the hydrogen ion exponent (pH) was 8.26, with a minimum value of 8.15 and a maximum value of 8.3; whereas the average of the same number of readings made on the dialysate was slightly lower, pH being equal to 8.11. Of interest also is the fact that the two lowest readings were obtained in cases of cerebral injury, treated by decompression and the withdrawal by puncture of considerable amounts of fluid. It is not unlikely that the diminished alkalinity in these instances may have been due to dilution of the fluid by hypersecretion.

As compared with the hydrogen ion concentration of the dialysate of the cerebrospinal fluid, that of the blood obtained from the same patient was found to be much higher. In the six instances in the normal group in which the blood was also tested an average value for pH of 7.66 was obtained. Thus the hydrogen ion concentration of the blood in these cases was greater than that of the spinal fluid by the value of 0.45.

14. The standard test solutions were prepared for us by Hynson, Westcott and Company, Baltimore.

In connection with the reaction of the cerebrospinal fluid in health, there are several interesting physiologic problems which still await solution. One of these concerns the relationship between the normal functional activity of the nervous centers and the reaction of the fluid. Mott[2] proposes the view that after normal sleep the alkalinity may be slightly greater than at the end of a day's work, because of the production of acid substances resulting from nerve cell activity.

TABLE 2.—A Comparison of the Hydrogen Ion Concentration of Blood and Cerebrospinal Fluid

No. of Case	Reaction of Cerebrospinal Fluid Value of pH	Reaction of Cerebrospinal Fluid Dialysate, Value of pH	Reaction of Blood Dialysate, Value of pH
9	8.25	8.2	7.7
10	8.3	8.1	7.6
11	8.3	8.15	7.75
12	8.25	8.0	7.65
14	8.25	8.05	7.65
19	8.2	8.0	7.65
22	8.3	8.15	7.75
23	8.3	8.15	7.6
25	7.95	7.9	7.65
27	8.35	8.15	7.7
28	8.3	8.1	7.65
29	8.3	8.1	7.65
32	8.3	8.15	7.5
40	8.2	8.1	7.7
42	8.15	8.15	7.75
43	7.95	7.75	7.65
46	8.4	8.15	7.75
17	8.3	7.95	7.60
Average	....	8.07	7.66

Another problem of interest concerns the reaction of the cerebrospinal fluid in different loci. From the work of a number of observers it is now known that ventricular and subarachnoid fluids may differ in some important respects. It has been shown, for instance, that there is a slightly higher percentage of sugar in ventricular than in subarachnoid fluid, whereas the reverse is true of the albumin content; furthermore, that ventricular fluid may be richer in waste substances which may have been added to it during its passage through the sub-

arachnoid perivascular and perineuronal spaces.[15] The possibility may therefore be entertained that the two fluids, which differ in these marked particulars, may also show measurable differences in reaction.

The Reaction of Cerebrospinal Fluid and of Blood Compared.—In a previous paragraph it was pointed out that blood and spinal fluid obtained from the same patient at the same time may show a considerable difference in the hydrogen ion concentration as determined by the colorimetric method. In Table 2 are given eighteen instances in which such comparative data were obtained. The average value of the hydrogen ion concentration tested upon the dialysate of the spinal fluid was 8.07 as compared with 7.66 obtained in the case of the blood dialysate. Thus the ionization of blood tested in this way is greater than that of cerebrospinal fluid by the value of 0.41. It must be emphasized, however, that the need of resorting to dialysis doubtless introduces a source of error in the data given, for the reason that the two fluids dialyzed —blood and cerebrospinal fluid—are not chemically equivalent, the former containing a higher percentage of protein and colloids, both of which are known to influence the dispersion of electrolytes through porous membranes.[16] These considerations, however, do not affect the observation that the hydrogen ion concentration of the spinal fluid tested directly is lower than that of the blood.[17]

The Reaction of the Cerebrospinal Fluid in Disease.—In this paper the observations have been limited to those diseases in which lumbar puncture is ordinarily done as a routine measure either for diagnosis or treatment. Tables 3 and 4 include twenty-eight cases of syphilitic disease and of syphilitic affections of the nervous system in which the reaction of the spinal fluid was determined. The diagnosis in all of these patients was confirmed either by cytologic and chemical tests or by the routine Wassermann reaction of the blood and spinal fluid.

From an examination of Table 3 it will be noted that the average hydrogen ion concentration (pH) of the spinal fluid in primary and secondary cases of syphilis is equal to 8.26, while determinations of the dialysate give somewhat lower readings (pH=8.14). Similar readings made upon the dialysate of the blood in seven of these patients gave an average value of pH equal to 7.64, which is 0.5 lower than that obtained for the dialysate of the spinal fluid. By comparing these figures with those recorded in Table 1, it will be observed that these values do not differ widely from those obtained for normal fluids. The

15. Cushing, H.: Jour. Med. Research, 1914, xxxi, 12, 13, 15.

16. Ostwald, W.: A Handbook of Colloid Chemistry, Philadelphia, P. Blakiston's Sons, 1915, p. 219.

17. The hydrogen ion concentration of the blood determined by the hydrogen electrode averages 0.3×10^{-7}, or pH = 7.5. The value for pH^{+} obtained by the colorimetric method is 7.66.

TABLE 3.—The Hydrogen Ion Concentration of the Cerebrospinal Fluid in Syphilitic Disease

Number of Case	Date	Name	Age	Diagnosis	Hospital Number	Wassermann*	Cell Count	Nonne	Noguchi	Reaction of Cerebrospinal Fluid, Value of pH	Reaction of Spinal Fluid Dialysate, Value of pH	Reaction of Blood Dialysate, Value of pH
20	8/24/15	E. S.	53	Syphilis	6276	B. ++ S. F. —	1	0	0	8.3	8.15	....
21	8/26/15	A. L.	30	Syphilis, epilepsy	16934	B. + S. F —	1	0	0	8.3	8.25	....
22	9/21/15	C. B.	38	Optic atrophy	17446	B. — S. F. ft. +	1	0	0	8.3	8.15	7.75
23	10/ 7/15	M. F.	30	Chancre	14164	B. + S. F. —	2	0	0	8.3	8.15	7.6
24	10/ 7/15	L. D	28	Chancre	17950	B. + S. F. —	0	0	0	....	8.25	....
25	10/12/15	J. L.	30	Chancre	4485	B. ft + S. F. -	0	0	0	7.95	7.9	7.65
26	10/12/15	P. C	35	Retinitis	15779	B. — S. F —	3	0	0	8.1	8.05	....
27	10/14/15	J. L.	30	Secondary syphilis	18124	B. - S. F. —	0	0	0	8.35	8.15	7.7
28	10/14/15	M. S.	22	Chancre	18122	B. — S. F. —	3	0	0	8.3	8.1	7.65
29	10/14/15	F C.	43	Chancre	17834	B. +++ S. F. —	56	+	+	8.3	8.1	7.65
30	10/23/15	L. W.	..	Mental symptoms	18355	B. + S. F. —	2	0	0	....	8.25	....
31	11/16/15	C. W	39	Syphilis, syphilitic gastritis (?)	18820	B. +++ S. F. —	1	0	0	8.3	8.25	....
32	11/18/15	W.	24	Chancre	18402	B. ++ S. F. —	0	0	0	8.3	8.15	7.5
33	10/19/15	C. E	18	Secondary syphilis	17043	B. +++ S. F. —	173	+	+	8.3	8.05	....
Averages							.....	.....	.....	8.26	8.14	7.64

* B. means blood; S. F. means spinal fluid.

results show, further, that in both groups the hydrogen ion concentration of the blood obtained from the same patient at the same time and similarly tested is in each instance greater than that of the spinal fluid, the average value for pH in the syphilitic cases being almost identical with that obtained in the normal cases.

Nor was any marked alteration of the normal reaction observed in the spinal fluid obtained from patients with syphilitic affections of the central nervous system, such as tabes, general paresis and cerebrospinal syphilis. The average values for pH in this group, as recorded in Table 4, are slightly lower than the normal, but the differences are too small to be of real significance. A study of the reaction of the fluid in these cases brings up an interesting point, namely, the relationship between inflammatory conditions of the meninges and the reaction of the cerebrospinal fluid. Some authors[15, 18] entertain the view that in the presence of infection acid products are formed which render the cerebrospinal fluid acid. From the presence of a high cell count, that is, an average thirty-five cells with a maximum of 110 cells, in the spinal fluid of most of these patients, one may assume a chronic inflammatory condition to have existed; and yet no alteration in reaction was demonstrable. This, however, does not preclude the possibility that acute inflammatory conditions may be associated with a more acid reaction, that is, with an increase in the hydrogen ion concentration. So far as we are aware no positive proof has been brought forth to show that acid substances may form in acute inflammatory conditions of the meninges, and that these may produce an acidulation of the cerebrospinal fluid.

The possibility that the reaction of the fluid may be rendered more acid in cases of infection suggests a therapeutic problem of considerable importance. As has been shown by Crowe[19] hexamethylamin is one of the few antiseptic drugs which can traverse the barrier of the choroid plexuses and pass from the blood stream into the cerebrospinal fluid. But in order to be effective in antagonizing infection, hexamethylenamin must, according to more recent studies,[20] be broken up into formaldehyde. This chemical change can occur only in an acid medium. Unless, therefore, it can be demonstrated that the spinal fluid becomes acidulated in the presence of infecting organisms and that hexamethylenamin is actually broken up into formaldehyde, considerable doubt must be entertained concerning the bactericidal power of this drug in combating infections of the meninges.

---

18. Wingrave, W.: Jour. Laryngol., Rhinol. and Otol., 1915, xxx, 270.

19. Crowe, S. J.: Bull. Johns Hopkins Hosp., 1909, xx, 102.

20. Burnam, C. F.: The Archives Int. Med., 1912, x, 324. Hinman, F.: Jour. Am. Med. Assn., 1913, lxi, 1601.

TABLE 4.—THE HYDROGEN ION CONCENTRATION OF THE CEREBROSPINAL FLUID IN SYPHILITIC AFFECTIONS OF THE NERVOUS SYSTEM INCLUDING TABES, GENERAL PARESIS AND CEREBROSPINAL SYPHILIS

Number of Case	Date	Name	Age	Diagnosis	Hospital Number	Wassermann*	Cell Count	Nonne	Noguchi	Reaction of Cerebrospinal Fluid, Value of pH	Reaction of Spinal Fluid Dialysate, Value of pH	Reaction of Blood Dialysate, Value of pH
34	8/24/15	H. V.	39	Tabes dorsalis.....	16893	B. +++ S. F. ++	24	St +	+	8.3	8.15	....
35	8/28/15	L. K.	46	Taboparesis.....	16953	B. — S. F. —	4	0	0	8.3	8.25	....
36	10/12/15	P. A. R.	57	Tabes dorsalis.....	House 10023	B. + S. F. —	0	0	0	8.1	8.0	....
37	8/24/15	N. L.	37	Cerebrospinal syphilis....	307	B. +++ S. F. +++	42	—	—	7.95 7.95	7.75 7.75	....
38	8/25/15	J. J.	50	Cerebrospinal syphilis....	16944	B. — S. F. ++	60	—	—	8.3	8.15	....
39	8/26/15	J B.	46	Cerebrospinal syphilis....	16711	B. +++ S. F. ?	110	—	—	8.25	8.15	....
40	8/31/15	S. T.	52	Cerebrospinal syphilis....	17037	B. +++ S. F. —	2	0	0	8.2	8.1	7.7
41	10/ 7/15	D. C.	31	Myelitis luetica.....	14164	B. — S. F. —	3	0	0	8.25	8.2	....
42	10/ 7/15	H. W.	56	Cerebrospinal syphilis....	14600	B. — S. F. +++	18	0	0	8.15	8.15	7.75
43	10/12/15	G. F.	42	Cerebrospinal syphilis....	17885	B. ++ S. F. ?	57	—	—	7.95	7.75	7.65
44	10/19/15	W. S.	47	Cerebrospinal syphilis....	18140	B. +++ S. F. +++	51	—	—	....	8.1	....
45	11/16/15	H. Y.	52	Cerebrospinal syphilis....	18641	B. — S. F. +	32	—	—	8.4	8.35	....
46	12/ 8/15	C. A.	36	Cerebrospinal syphilis....	19447	B. ? S. F. +++	28	—	—	8.4	8.15	7.75
47	12/18/15	S. J.	29	Cerebrospinal syphilis....	19921	B. + S. F. ?	28	0	0	8.3	7.95	7.60
Averages.....						.....	35	.....	.....	8.22	8.08	7.69

* B. means blood; S. F. means spinal fluid.

CONTENTS OF VOLUME XVII

APRIL, 1916. NUMBER 4

Studies of Edema in Pneumonia. Mary E. Maver and A. B. Schwartz, Chicago.

Hypoglycemia and Progressive Muscular Dystrophy. R. H. McCrudden, M.D., and C. S. Sargent, S.B., Boston.

A Clinical Study of Delayed Gastric Emptying Based on 185 Consecutive Cases Occurring in an Unselected Series of 1,600 Patients with Digestive Symptoms. I. H. Levy, M.D., and J. L. Kantor, M.D., Syracuse.

Further Studies of Biological Methods for the Diagnosis of Tuberculosis. J. Bronfenbrenner, Ph.D., Morris H. Kahn, M.D., J. Rockman, M.D., and Max Kahn, M.D., Ph.D., Pittsburgh.

Two Additional Cases of Miliary Tuberculosis of the Placenta with Clinically Latent Tuberculosis of the Mother. Carl Vernon Weller, M.D., Ann Arbor, Mich.

Progressive Lipodystrophy. Charles Herrman, M.D., New York.

A Study of the Buffer Value of the Blood. R. L. Levy, M.D., Baltimore, and L. G. Rowntree, M.D., Minneapolis.

An Adaptation of the Erlanger Capsule to any Polygraph for Obtaining Arterial Pulse Records. Robert H. Halsey, M.D., New York.

A Study of the Blood in Hemophilia. S. H. Hurwitz, M.D., and W. P. Lucas, M.D., San Francisco.

The Significance of the Uric Acid, Urea and Creatinin of the Blood in Nephritis. Victor C. Myers, Ph.D., and Morris S. Fine, Ph.D., with the Cooperation of Walter G. Lough, M.D., New York.

The Effects of Suprarenal Feeding. R. G. Hoskins, Ph.D., and Augusta D. Hoskins, A.M., Chicago.

Book Review: Pathogenic Micro-Organism, Including Bacteria and Protozoa.

MAY, 1916. NUMBER 5

Multiple Abscesses of the Brain in Infancy. James B. Holmes, M.D., Baltimore.

Studies on the Pineal Gland. Gilbert Horrax, M.D., Boston. I. Experimental Observations; II. Clinical Observations.

The Adjustment of Pressure in Induced Pneumothorax. With Special Regard to the Mobility of the Mediastinum as Indicated by the Manometer. C. D. Parfitt, M.D., Gravenhurst, Ont.

Sino-Auricular Block Due to Tobacco Poisoning. Selian Neuhof, M.D., New York.

Observations on the Typhoidin Reaction. Charles R. Austrian, M.D., and Arthur L. Bloomfield, M.D., Baltimore.

Studies of the Heart's Functional Capacity as Estimated by the Circulatory Reaction to Graduated Work. Theodore B. Barringer, Jr., M.D., New York.

The Present Status of Magnesium Sulphate in the Treatment of Tetanus. H. E. Robertson, M.D., Minneapolis.

The Basal Metabolism in Obesity. James H. Means, M.D., Boston.

JUNE, 1916. NUMBER 6. PART 1

A Study of Salt, Nitrogen and Water Excretion in Nephritis. James P. O'Hare, M.D., Boston.

Experimental Hypercholesterolemia. Kaethe Dewey, M.D., Chicago.

A Pharmacologic and Clinical Study of Papaverin. David I. Macht, M.D., Baltimore.

The Use of the "Karell Cure" in the Treatment of Cardiac, Renal and Hepatic Dropsies. Edward Harris Goodman, M.D., Philadelphia.

On the Reaction of the Cerebrospinal Fluid. S. H. Hurwitz, M.D., and C. L. Tranter, M.D., San Francisco.

A Clinical Hemoglobinometer. Herbert Haessler and Harry S. Newcomer, M.D., Philadelphia.

A Method for the Determination of the Alkali Reserve of the Blood Plasma. W. McK. Marriott, M.D., Baltimore.

Book Reviews:

Diseases of the Digestive Organs with Special Reference to Their Diagnosis and Treatment. Charles D. Aaron, Sc.D., M.D.

Changes in the Food Supply and Their Relation to Nutrition. Lafayette B. Mendel.

JUNE, 1916. NUMBER 6. PART 2

Clinical Calorimetry. Ninth Paper. Further Measurements of the Surface Area of Adults and Children. Margaret Sawyer, B.S., Iowa City, Iowa, Richard H. Stone and Eugene F. DuBois, M.D., New York.

Clinical Calorimetry. Tenth Paper. A Formula to Estimate the Approximate Surface Area if Height and Weight Be Known. Delafield Du Bois, B.S., Burlington, Vt., and Eugene F. Du Bois, M.D., New York.

Clinical Calorimetry. Eleventh Paper. A Comparison of the Metabolism of Men Flat in Bed and Sitting in a Steamer Chair. G. F. Soderstrom, A. L. Meyer, M.D., and

Clinical Calorimetry. Twelfth Paper. The Metabolism of Boys 12 and 13 Years Old Compared with the Metabolism at Other Ages. Eugene F. Du Bois, M.D., New York.

Clinical Calorimetry. Thirteenth Paper. The Basal Metabolism of Normal Adults with Special Reference to Surface Area. Frank C. Gephart, A.B., and Eugene F. Du Bois, M.D., New York.

Clinical Calorimetry. Fourteenth Paper. Metabolism in Exophthalmic Goiter. Eugene F. Du Bois, M.D., New York.
E. F. Du Bois, M.D., New York.

Clinical Calorimetry. Fifteenth Paper. The Basal Metabolism in Pernicious Anemia. A. L. Meyer, M.D., and Eugene F. Du Bois, M.D., New York.

Clinical Calorimetry. Sixteenth Paper. The Basal Metabolism of Patients with Cardiac and Renal Disease. Francis W. Peabody, M.D., Boston, A. L. Meyer, M.D., and Eugene F. Du Bois, M.D., New York.

Clinical Calorimetry. Seventeenth Paper. Metabolism and Treatment in Diabetes. Frederick M. Allen, M.D., and Eugene F. Du Bois, M.D., New York.

Index to Volume XVII.

CONTENTS

A Study of Salt, Nitrogen and Water Excretion in Nephritis. James P. O'Hare, M.D., Boston 711

Experimental Hypercholesterolemia. Kaethe Dewey, M.D., Chicago.. 757

A Pharmacologic and Clinical Study of Papaverin. David I. Macht, M.D., Baltimore 786

A Clinical Hemoglobinometer. Herbert Haessler and Harry S. Newcomer, M.D., Philadelphia 806

The Use of the "Karell Cure" in the Treatment of Cardiac, Renal and Hepatic Dropsies. Edward Harris Goodman, M.D., Philadelphia 809

On the Reaction of the Cerebrospinal Fluid. S. H. Hurwitz, M.D., and C. L. Tranter, M.D., San Francisco 828

A Method for the Determination of the Alkali Reserve of the Blood Plasma. W. McK. Marriott, M.D., Baltimore 840

Book Reviews:

Diseases of the Digestive Organs with Special Reference to Their Diagnosis and Treatment. Charles D. Aaron, Sc.D., M.D.... 852

Changes in the Food Supply and Their Relation to Nutrition. Lafayette B. Mendel 853

The Archives of Internal Medicine is issued monthly. Two volumes are published annually.

Manuscripts offered for publication and other correspondence relating to the editorial management of The Archives should be sent to Dr. Joseph L. Miller, 122 South Michigan Boulevard, Chicago. Communications regarding subscriptions, reprints, etc., should be addressed to The Archives of Internal Medicine, American Medical Association, 535 North Dearborn Street, Chicago.

Footnotes and bibliographies should conform to the style of the Index Medicus or to that of the Index-Catalogue of the Surgeon-General's Library. It is specially requested that the titles of articles and the exact date of issues, year, volume and page, be given in each case. Contributors are requested not to furnish bibliographies which are unnecessary, or mere clerical compilations. On receipt of 10 cents the American Medical Association will send a pamphlet entitled "Suggestions to Medical Authors," containing suggestions to authors on the preparation of manuscripts, rules for footnotes and bibliographies and a list of several hundred medical periodicals of the world with approved abbreviations of each.

Authors will receive one hundred reprints free; additional copies may be obtained at cost.

The domestic subscription price per year of two volumes is $4.00; Canadian rate $4.25; foreign rate $4.40 (18 shillings, 18 marks, 22 francs); including postage. Single copies 50c postpaid.

Make checks, etc., payable to the AMERICAN MEDICAL ASSOCIATION.